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(71) Applicant *(for all designated States except US)*: **SIMON FRASER UNIVERSITY** [CA/CA]; Industry Liaison Office, Room 2100, Strand Hall, Burnaby, British Columbia V5A 1S6 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BRANDA, Neil R.** [CA/CA]; 1045 Prospect Avenue, North Vancouver, British Columbia V7R 2M6 (CA). **WUESTENBERG, Bettina** [DE/DE]; Stubbener Strasse 75, 27721 Ritterhude (DE). **LEMIEUX, Vincent** [CA/CA]; 116 Rue Lavigne, Mont-tremblant, Québec J8E 1J9 (CA). **ADAMS, Michael** [CA/CA]; 605-1068 Hornby Street, Vancouver, British Columbia V6Z 3Y2 (CA). **GAUTHIER, Simon** [CA/CA]; 12 Western Avenue, Ottawa, Ontario K1Y 0L4 (CA).

(74) Agents: **BAILEY, Thomas W.** et al.; 480 The Station, 601 West Cordova Street, Vancouver, British Columbia V6B 1G1 (CA).

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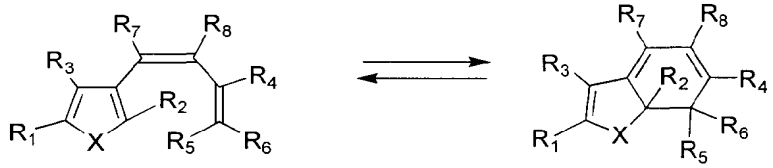

I(o) I(c)

(57) Abstract: Novel photochromic and electrochromic hexadiene compounds are described. The compounds are reversibly convertible between ring-open and ring-closed isomeric forms as indicated in structures I(o) and I(c) below. (See formula in original abstract of application) The conversion between the different isomeric forms may be induced by light or electricity. In one embodiment the compounds may include a charge transfer moiety including electron donor and acceptor groups. The electron donor and acceptor are linearly conjugated in the ring-open form to enable electron transfer but are electrically insulated in the ring-closed form. Methods for synthesizing the compounds from photochemically and/or electrically inert precursors are also described. For example, the photoresponsive compounds may be synthesized by reacting diene precursors with dienophiles in a condensation reaction. The compounds may be utilized in reactivity-gated photochromic or electrochromic applications. In one embodiment of the invention, compounds of the invention may be used in a method to selectively release a releasable agent, such as a small molecule. According to this method, a photochemically inert precursor compound is reacted with the releasable agent to form a carrier compound comprising a switching moiety, the switching moiety being reversibly convertible between a thermally unstable form and a thermally stable form. The switching moiety may be selectively converted between the first and second forms to cause controlled release of the releasable agent from the carrier compound.

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PHOTOCHROMIC AND ELECTROCHROMIC COMPOUNDS AND SYNTHESIS AND USE THEREOF

Related Application

[0001] This application claims the benefit of the filing date of United States provisional patent application no. 60/684,715 filed 25 May 2005 which is hereby incorporated by reference.

Technical Field

[0002] This application relates to novel photochromic and electrochromic compounds, methods of making the compounds, and uses thereof.

Background

[0003] Photochromism is defined as the reversible photoinduced transformation of a chemical species between two isomers having different absorption spectra [1]. The photochemical reaction is accompanied by a difference in properties other than the absorption of light such as the emission of light, refractive index, polarization, redox potentials, dipole moments, host-guest interactions and chemical reactivity. The changes in these properties implies that photoresponsive compounds can contribute to the advancement of numerous, diverse applications, where it is desirable that a given property is regulated. Applications include, but are not limited to, photonic devices such as (1) actinometers, (2) sensors and dosiometers, (3) novelty items such as inks, paints and other dyes, (4) variable transmission filters, (5) optical information storage systems, (6) molecular switches that can be incorporated into molecule-based wires, circuitry and machinery, (7) opto-electronic systems, (8) reversible holographic systems, (9) electro-optical devices such as waveguides, (10) the light-induced delivery of biologically, medically and synthetically relevant compounds, and (11) photoregulation of polymers.

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[1] *Organic Photochromic and Thermochromic Compounds*; Crano, J. C., Guglielmetti, R. J., Eds.; Plenum Press: New York, 1999; Vols. 1 and 2. M. Irie, in *Molecular Switches*, (Ed.: B. L. Feringa), Wiley-VCH, Weinheim, Germany, **2001**, pp. 37–62; Special issue on photochromism: M. Irie, *Chem. Rev.* **2000**, *100*, 1685–1716.

[0004] Electrochromic molecules which change color when electrochemically oxidized or reduced are also well known in the prior art [2]. For example, compounds exhibiting electrochomism, including "dual mode" compounds having both electrochromic and photochromic properties, are described in applicant's PCT application No. PCT/CA2003/001216 (WO 2004/015024) which is hereby incorporated by reference.

[0005] Numerous optical technologies such as waveguiding, data storage, variable reflectance in eyewear and filters, and sensors rely on the non-linear optical (NLO) properties of materials [3]. There has been a recent and enormous growth in the interest in NLO materials and some estimates claim that over one third of the existing electronic technologies currently used for data transmission and processing will be replaced by the faster electro-optic and photonic analogues. The success of these devices requires the development of new functional NLO materials with large and rapid NLO responses. NLO properties originate from molecules that have strong charge transfer excitations within non-centrosymmetric structures due to a polarisable π-conjugated framework, where electron donor ('D') and acceptor ('A') groups at the ends of the linear π-pathway creates an asymmetric charge distribution.

[0006] In systems that undergo "gated" photochromism, irradiation with light does not trigger a molecular transformation unless another external stimulus such as electricity, other photons, heat, or a chemical is applied before or during the irradiation period. By combining more than one input stimulus in molecular switching technologies, "logic-based" devices can be developed. In reactivity-gated photochromism or electrochromism, an initial chemical reaction must occur to convert the compound from a non-photo- or electroactive state to a photo- or electroactive

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[2] *Electrochromism: Fundamentals and Applications*, Monk, P. M. S.; Mortimer, R. J.; Rosseinky, D. R., Eds., VHC: New York, 1995.

[3] Di Bella, S. *Chem. Soc. Rev.* **2001**, *30*, 355. Verbiest, T.; Houbrechts, S.; Kauranen, M.; Clays, K.; Persoons, A. *J. Mater. Chem.* **1997**, *7*, 2175.

state. Such systems may be particularly useful for sensing and dosiometry applications.

[0007] Molecular architectures that incorporate the 1,3,5-hexatriene motif are often photoresponsive and undergo reversible ring-closing and ring-opening reactions. Hexatriene compounds such as diarylethenes make up an important class of photoswitchable compounds [4] and many of the derivatives are also electroactive [5]. These particular compounds typically undergo thermally irreversible photoreactions with a high degree of fatigue resistance. They are the focus of numerous current research efforts. Previous reports of reactivity-gated photochromism using diarylethenes describe systems that operate based on the fact that the presence of the gate input affects the quantum yield of the ring-closing and ring-opening reactions by biasing the conformational equilibrium of the systems [6]. In many cases the effects are small.

[0008] The development of novel variations of the versatile 1,3,5-hexatriene architecture and convenient methods to prepare them is an important goal. The incorporation of a donor-π-acceptor motif (D- π-A) which can be reversibly created

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[4] M. Irie, in *Molecular Switches*, (Ed. B. L. Feringa), Wiley-VCH, Weinheim **2001**, 37-60.

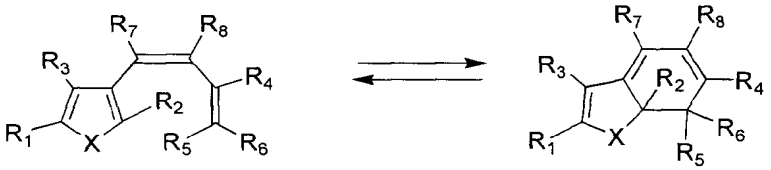
[5] Peters, A.; Branda, N. R. *Chem. Commun.* **2003**, 954. Gorodetsky, B.; Samachetty, H.; Donkers, R. L.; Workentin, M. S.; Branda, N. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 2812. Koshido, T.; Kawai, T.; Yoshino, K. *J. Phys. Chem.* **1995**, *99*, 6110. Peters, A. Branda, N. R. *J. Am. Chem. Soc.* **2003**, *125*, 3404. Zhou, X.–H.; Zhang, F.–S.; Yuan, P.; Sun, F.; Pu, S.–Z.; Zhao, F.–Q.; Tung, C.–H. *Chem. Lett.* **2004**, *33*, 1006. Moriyama, Y.; Matsuda, K.; Tanifuji, N.; Irie, S.; Irie, M. *Org. Lett.* **2005**, *7*, 3315. Brown, W. R.; de Jong, J. J. D.; Kudernac, T.; Walko, M.; Lucas, L .N.; Uchida, K.; van Esch, J. H.; Feringa, B. L. *Chem. Eur. J.* **2005**, *11*, 6414. Brown, W. R.; de Jong, J. J. D.; Kudernac, T.; Walko, M.; Lucas, L. N.; Uchida, K.; van Esch, J. H.; Feringa, B. L. *Chem. Eur. J.* **2005**, *11*, 6430. Guirado, G.; Coudret, C.; Hliwa, M.; Launay, J.–P. *J. Phys. Chem. B.* **2005**, *109*, 17445. Tsujioka, T.; Kondo, H. *App. Phys. Lett.* **2004**, *83*. 937.

[6] Takeshita, M.; Irie, M. *J. Chem. Soc., Chem. Comm.* **1996**, 1807. Takeshita, M.; Soong, C. F.; Irie, M. *Tetrahedron Lett.* **1998**, *39*, 7717. Irie, M.; Miyatake, O.; Uchida, K.; Eriguchi, T. *J. Am. Chem. Soc.* **1994**, *116*, 9894.

and broken in a controlled manner as part of the photochromic reaction of the novel architecture would be advantageous for the development of new functional NLO materials. It would also be beneficial to develop new compounds suitable for reactivity-gated photochromism or electrochromism, including gated systems enabling controlled release of small molecules and the like.

Summary of Invention

[0009] This application relates to the structure, synthesis, characterization and use of a series of novel hexatriene compounds. In one embodiment, each compound of the invention is reversibly convertible between a first ring-open isomeric form represented by the formula I(o) and a second ring-closed isomeric form represented by I(c)



I(o) I(c)

wherein X is a heteroatom selected from the group consisting of S, N and O; R_1 is selected from the group consisting of H, a halogen, alkyl, aryl and substituted aryl; R_2 is selected from the group consisting of alkyl, aryl and substituted aryl; R_3 is selected from the group consisting of H and alkyl; R_4 is selected from the group consisting of H, alkyl, aryl, substituted aryl, an electron-donating group, an electron-accepting group, and a constituent of an optionally substituted heterocycle; R_5 is selected from the group consisting of alkyl, aryl, substituted aryl, an electron-donating group and an electron-accepting group; R_6 is selected from the group consisting of alkyl, aryl, substituted aryl, an electron-donating group, an electron-accepting group and a constituent of an optionally substituted heterocycle; and R_7 and R_8 are each selected from the group consisting of a constituent of a 5 membered ring comprising H or a halogen or an optionally substituted 6 membered ring. In an embodiment when R_4 and R_6 are constituents of a thiophene ring and R_5 is an alkyl, aryl or substituted aryl, then R_7 and R_8 are constituents of an optionally substituted 6 membered ring. In another embodiment when R_7 and R_8 are constituents of a 5 membered halogenated ring, then R_4, R_5 and R_6 are independently not an alkyl or aryl.

[00010] The hexatriene compound represented by formula I(o) is reversibly convertible between the first and second forms in response to a light and/or electrical stimulus. For example, compound I may be converted from the first form to the second form by the application of ultraviolet light and from the second form to the first form by visible light.

[00011] In one embodiment of the invention, the compound may include both a charge transfer moiety comprising an electron donor and an electron acceptor and a switching moiety reversibly convertible between a first ring-open form and a second ring-closed form in response to a light or electrical stimulus. In this embodiment the electron donor and electron acceptor are linearly conjugated when the switching moiety is in the first form and electronically insulated when the switching moiety is in the second form. Accordingly, the charge transfer and isomeric switching functionalities of the compound are effectively integrated.

[00012] In one embodiment of the invention, compounds of the invention may be used in a method to selectively release a releasable agent, such as a small molecule. According to this method, a photochemically inert precursor compound is reacted with the releasable agent to form a carrier compound comprising a switching moiety, the switching moiety being reversibly convertible between a thermally unstable form and a thermally stable form. The switching moiety may be selectively converted between the first and second forms to cause controlled release of the releasable agent from the carrier compound. The gated reaction between the precursor and the releasable agent may be, for example, a reversible condensation reaction.

[00013] Methods for synthesizing the hexatriene compounds of the invention and precursors thereof are also described.

Brief Description of Drawings

[00014] In drawings which are intended to illustrate embodiments of the invention:

[00015] Figure 1 are graphs showing changes in the UV-VIS absorption spectra of solutions of compounds **10–17** when irradiated with 365-nm light (313 nm for **12**). The solvent, concentrations and total irradiation times for each compound are provided in the figure.

[00016] Figure 2 are graphs showing the modulated absorptions of the ring-open isomers (□) and the ring-closed isomers (●) during alternating UV and VIS irradiations. The irradiation wavelengths and times for each compound are provided in the figure.

[00017] Figure 3A is a graph showing changes in the UV–VIS absorption spectra when an acetonitrile solution (2×10^{-5} M) of **26** is irradiated with 313-nm light for a total of 45 seconds (solid lines) and 254-nm light for 45 seconds (dashed line).

[00018] Figure 3B is a graph showing changes in the UV–VIS absorption spectra when an acetonitrile solution (2×10^{-5} M) of **27** is irradiated with 313-nm light for a total of 45 seconds (solid lines) and 254-nm light for 45 seconds (dashed line).

[00019] Figure 4A is a picture showing the color change that occurs when a DMSO solution of diene **25** and excess maleic anhydride are mixed and exposed to 313-nm light (right spot). The left spot is a sample containing only the diene **25** that has been simultaneously irradiated. Cyclohexadiene **25** (1 mg) was added to a saturated solution of maleic anhydride in DMSO (0.5 mL) and a small amount of DMSO was added (~0.5 mL) to dissolve the remaining solid. A solution containing only the cyclohexadiene was also prepared (1 mg in 1 mL). One drop of each solution was deposited on a microscope slide and placed on a heating stage at 35 °C for 30 minutes. After this heating period, the samples were simultaneously irradiated for 30 seconds with 313-nm light. The sample containing maleic anhydride and the cyclohexadiene turned yellow. The other did not. The same behaviour was observed when the solution of maleic anhydride and cyclohexadiene and the control solution were kept at room temperature for 14 hours.

[00020] Figure 4B shows the same sample of diene **25** and maleic anhydride after bleaching with greater than 415-nm light.

[00021] Figure 5 are graphs showing the insignificant changes in the UV-VIS absorption spectra when CH_2Cl_2 solutions of the non-photoactive compounds **32** and **33** are irradiated with UV light. In the case of **32**, the light source was changed to > 490 nm after 60 seconds.

[00022] Figure 6 is a graph showing changes in the UV–VIS absorption spectra when a CH_2Cl_2 solution (2.5×10^{-5} M) of the product obtained from the thermal reaction of fulvene **32** and maleic anhydride is irradiated with 313-nm light for a total of 60 seconds.

[00023] Figure 7 are UV-VIS absorption spectra: (a) UV–VIS absorption spectra of a CH_2Cl_2 solution (3.4×10^{-5} M) of the ring-closed isomer **36** and a 1:1 mixture of **32** and diethyl dicyanofumarate obtained after the irradiation of **36** with light of wavelengths greater than 490 nm. (b) UV–VIS absorption spectra of a CH_2Cl_2 solution (3.4×10^{-5} M) of the ring-closed isomer **37** and a 1:1 mixture of **33** and diethyl dicyanofumarate obtained after the irradiation of **37** with light of wavelengths greater than 434 nm. (c) The UV–VIS absorption spectrum of a 1:1 mixture (in CH_2Cl_2) of the ring-closed compounds **36** and **37** before (dark grey) and after irradiation with 430-nm light (light grey) to selectively ring-open **37**. (d) The UV–VIS absorption spectrum of a 1:1 mixture (in CH_2Cl_2) of the ring-closed compounds **36** and **37** before (dark grey) and after irradiation with 557-nm light (light grey) to selectively ring-open **36**. (e) The UV–VIS absorption spectrum of a 1:1 mixture (in CH_2Cl_2) of the ring-closed compounds **36** and **37** before (dark grey) and after irradiation with light greater than 434 nm (light grey) to ring open both compound.

[00024] Figure 8 are partial ^1H NMR (500 MHz, CD_2Cl_2) spectra showing the peaks corresponding to the aromatic protons in (a) fulvene **32**, (b) a 1:1 mixture of **32** and diethyl dicyanofumarate measured when the equilibrium with **34** has been reached, (c) the isolated mixture of ring-closed stereoisomers **36** and (d) a solution of **36** that has been periodically irradiated with greater than 490 nm light showing the

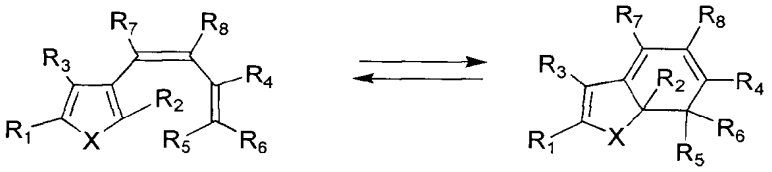
disappearance of the ring-closed compounds **36** and the appearance of fulvene **32**. The partial ^{1}H NMR spectra of (e) a 1:1 mixture of **36** and **37** before irradiation (f) after irradiating with 430-nm light to partially ring-open compound **37**, (g) after irradiating the same sample with greater than 557-nm light to partially ring-open compound **36** and (h) after irradiating the same sample with greater than 434-nm light to fully ring-open both compounds.

Description

[00025] Throughout the following description, specific details are set forth in order to provide a more thorough understanding of the invention. However, the invention may be practiced without these particulars. In other instances, well known elements have not been shown or described in detail to avoid unnecessarily obscuring the invention. Accordingly, the specification and drawings are to be regarded in an illustrative, rather than a restrictive, sense.

General Chemical Structure of Isomeric Hexatriene Compounds

[00026] This application relates to hexatriene compounds and methods of synthesizing and using same. As shown in Scheme 1 below, each compound of the invention is reversibly convertible between a ring-open isomeric form I(o) and a ring-closed isomeric form I(c):



I(o) I(c)

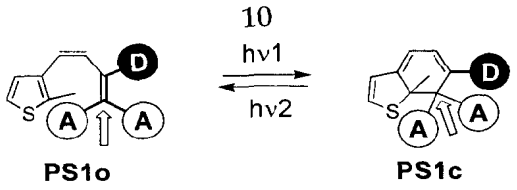
Scheme 1

As described further below, the conversion between the isomeric forms I(o) and I(c) may be triggered by light and/or an electrical stimuli. For example, conversion from the ring-open form to the ring-closed form may be triggered by ultraviolet light and conversion from the ring-closed form to the ring-open form may be triggered by visible light.

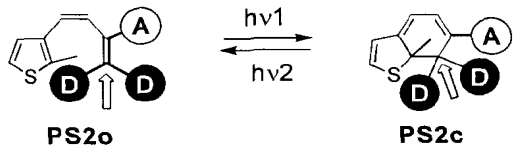
[00027] The $R_1 - R_7$ substituents of compound (I) may vary without departing from the invention. For example, X may be a heteroatom such as S, N and O; R_1 may be H, a halogen, alkyl, aryl and substituted aryl; R_2 may be alkyl, aryl and substituted aryl; R_3 may be H and alkyl; R_4 may be H, alkyl, aryl, substituted aryl, an electron-donating group, an electron-accepting group, and an optionally substituted constituent of a heterocycle; R_5 may be alkyl, aryl, substituted aryl, an electron-donating group and an electron-accepting group; R_6 may be alkyl, aryl, substituted aryl, an electron-donating group, an electron-accepting group and an optionally substituted constituent of a heterocycle; and R_7 and R_8 may be a constituent of a 5 membered ring comprising H or a halogen or an optionally substituted 6 membered ring. In a particular embodiment where R_4 and R_6 are constituents of a thiophene ring and R_5 is an alkyl, aryl or substituted aryl, then R_7 and R_8 are constituents of an optionally substituted 6 membered ring. In another embodiment where R_7 and R_8 are constituents of a 5 membered halogenated ring, then R_4, R_5 and R_6 are independently not an alkyl or aryl.

Charge Transfer Moiety

[00028] As indicated above, substituents $R_4 - R_6$ may optionally include electron-donating and electron-accepting groups. This feature is described more fully in the generalized structures shown in Schemes 2 and 3 below. In this embodiment of the invention, charge transfer between the electron-donating group(s) 'D' and the electron-accepting group(s) 'A' is regulated by photo-induced switching of the hexatriene compound between the ring-open and ring-closed isomeric forms.



Scheme 2



Scheme 3

[00029] With reference to Schemes 1 and 2, R_4 may be an electron-donating group 'D' and R_5 and R_6 may be electron-accepting groups 'A'. Only in the ring-open isomer (PS1o) are the 'D' and 'A' groups electronically connected to each other by an alkene creating a D–π–A motif. In the ring-closed isomer (PS1c), the 'A' and 'D' groups are electronically insulated from each other and the D–π–A motif has been removed. Similarly, with reference to Schemes 1 and 3, R_4 may be an electron-accepting group 'A' and R_5 and R_6 may be electron-donating groups 'D'. Only in the ring-open isomer (PS2o) are the 'D' and 'A' groups electronically connected to each other by an alkene creating a D–π–A motif. In the ring-closed isomer (PS2c), the 'A' and 'D' groups are electronically insulated from each other and the D–π–A motif has been removed. In both examples the ring-closing reaction triggered by irradiation with a particular wavelength of light (*hv1*) causes a change in hybridization of one of the carbons (highlighted by the arrows in Schemes 2 and 3 above) connecting the donating group to the accepting group thus resulting in the break in the linear π–conjugation. The reverse reaction and the reconstruction of the D–π–A motif can be triggered by a different wavelength of light (*hv2*).

[00030] The installation of electron donor and acceptor groups at the ends of a linear π backblone in the ring-open embodiment creates an asymmetric charge distribution. As mentioned above, structures having a polarisable π-conjugated

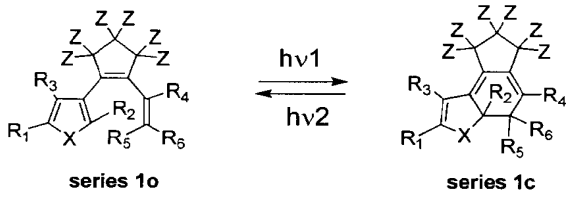
framework may be suitable for NLO applications. The photoswitching of the donor–π–acceptor systems has the potential to significantly impact opto-electronic, electro-optic and photonic devices and materials.

[00031] As described further below, the invention encompasses synthetic methods for spatially installing different donor and acceptor groups on the photoresponsive hexatriene backbone. For example, with reference to Scheme 2, donor 'D' on PS1o and PS1c may include alkyl groups or aromatic rings bearing electron-donor substituents (such as phenols, phenol ethers and anilines) or electron-donating heterocycles (such as thiophenes). Suitable acceptor groups 'A' on PS1o and PS1c could include carbonyl-based functional groups such as nitriles (CN). With reference to Scheme 3, donor 'D' on PS2o and PS2c may include electron-donating sulfides and acceptor 'A' may include aromatic rings bearing electron-withdrawing substituents (such as nitrobenzene) and heterocycles (such as pyridine). According to one synthetic scheme, hexatriene compounds comprising a charge transfer moiety including an electron donor and acceptor may be derived from the condensation of thiophene-functionalized aldehydes or ketones with activated methylene compounds or with ylides. Such carbonyl synthons offer a wide range of possible synthetic modifications and hence a large variety of electron donor and acceptor groups can be installed on the same structural backbone. The result is a convenient and modular method to produce numerous "made-to-order" photoresponsive materials from the same set of starting materials.

[00032] The general molecular architecture and synthetic route is particularly appealing since the D–π–A motif is positioned at the side of the hexatriene unit, which allows for the greatest amount of flexibility and tolerance in preparation and derivatization. Other photoresponsive D–π–A motifs based on dithienylethenes bear the donor and acceptor groups on the thiophene rings. This is less appealing since it limits how the molecule may be decorated with useful groups which impart the desired properties.

Pentene Ring Embodiment

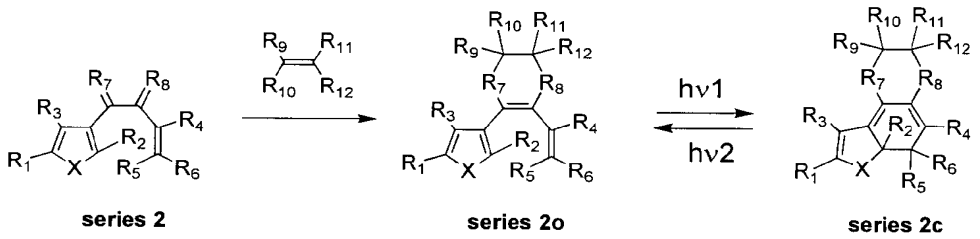
[00033] Scheme 4 illustrates a particular embodiment of the invention where R_7 and R_8 (as shown generally in Scheme 1 above) together comprise a pentene ring.



Scheme 4

In this example the Z substituents of the pentene ring may either be H or a halogen, such as fluorine. As in the other embodiments of the invention, the hexatriene compound is reversibly convertible between the ring-open and ring-closed isomeric forms by a light trigger, such as UV light and visible light. The wavelengths of light acting as conversion triggers may vary and may be "tuned" by decorating the molecular background with different functional groups.

Reactivity-Gated Photochromism and Electrochromisim



Scheme 5

[00034] Scheme 5 illustrates a representative process for producing a photoresponsive hexatriene compound of the invention from a condensation reaction between a diene precursor and a dienophile. In this example, the precursor is a butadiene and the dienophile is an alkene. The particular condensation reaction shown is a

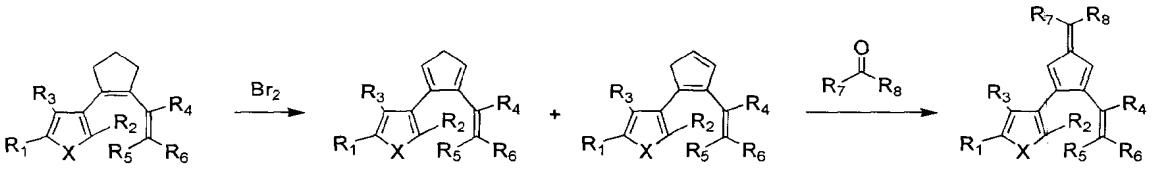
cycloaddition. The condensation reaction may, for example, consist of Diels-Alder [4+2] cycloaddition with the dienophile(s). As will be apparent to a person skilled in the art, many variations are possible without departing from the invention. According to the embodiment of Scheme 5, the initial butadiene is photochemically inert (i.e. it does not undergo a facile photoreaction). The butadiene precursor undergoes a thermally induced condensation reaction to produce a photoresponsive hexatriene reversibly convertible between different isometric forms as discussed above. The optical and electronic differences between the ring-open and ring-closed isomers can be used as a read-out signal to sense the presence of the dienophile and its dose. In this example the R_9, R_{10}, R_{11} and R_{12} substituents of the alkene may include H, alkyl, aryl, CN, CO_2-alkyl, CO_2-aryl, anhydride and imide.

[00035] Scheme 5 is an example of reactivity-gated photochromic system. That is, irradiation of the system with light does not trigger a molecular transformation unless another external "gate" stimulus, in this case a thermally induced condensation reaction, occurs prior to or during the irradiation period. As discussed above, in reactivity-gated photochromism or electrochromism, an initial chemical reaction must occur to convert the compound from a non-photo or non-electroactive state to a photo or electroactive state. Only after this initial reaction takes place can the compounds be photochemically interconverted between two isomers displaying unique properties such as, but not limited to, the absorption and emission of light, refractive index and other optical properties, redox properties, and topological properties.

[00036] Further with reference to Scheme 5, when the groups labeled 'R_4' and 'R_6' make up a heterocycle, such as a thiophene ring, the compounds resemble the dithienylethenes that are known to undergo photo- and electrochromic reactions and can be reversibly converted between their ring-open (**series 2o**) and ring-closed (**series 2c**) forms. Each isomer possesses unique properties already described for other photochromic compounds. This provides a variety of output signals that can be detected (e.g. color, redox potential, dipole moment, host-guest chemistry).

[00037] This technological approach is general and can be applied to a wide range of architectures as long as they are photostable and undergo mild reactions to produce

photoactive hexatriene architectures. For example, when the groups labeled as 'R_7' and 'R_8' in Scheme 5 are carbon, a wide variety of electrocyclization reactions are possible. These groups can also be a part of a cyclic or acyclic conjugated system. As will be apparent to a person skilled in the art, these compounds can be subjected to polymerization reactions to produce functional materials such as conjugated polymers. When they are a part of a pentadiene system, they may be deprotonated and undergo condensation reactions with other carbonyl compounds to produce novel butadienes as illustrated in Scheme 6, below, providing access to new methods to decorate these photo- and electro-responsive compounds with functionality.

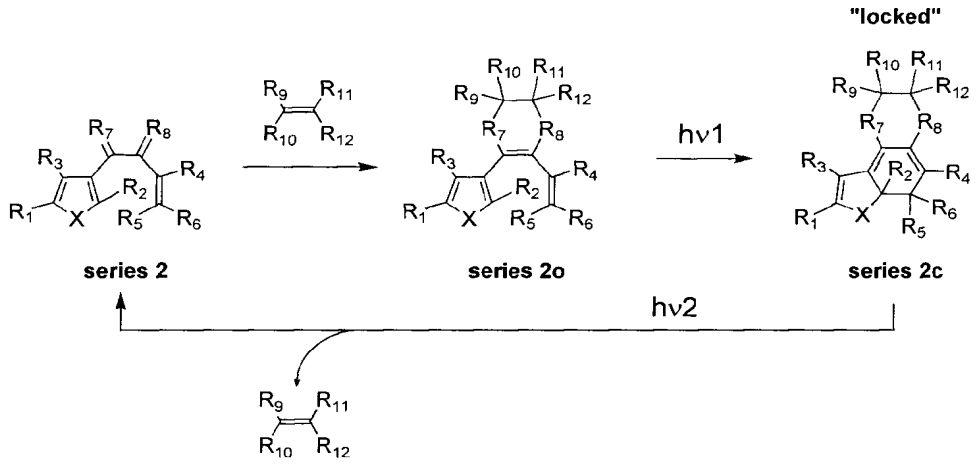


Scheme 6

The final product (FV) of the reactions of Scheme 6 is a fulvene. Fulvene FV may be prepared in a "one-pot" procedure without the need to isolate the cyclopentadiene intermediates (CPD1 and CPD2). In this embodiment the general synthetic scheme involves reacting the initial hexatriene (HT1) with bromine. The reaction product undergoes spontaneous elimination to generate a mixture of cyclopentadienes (CPD1 and CPD2). The cyclopentadienes may be condensed with aldehydes and ketones to generate the final fulvenes FV. In this example R_7 and R_8 may comprise H, alkyl, substituted alkyl, aryl and substituted aryl.

Selective Release of Reactants

[00038] Scheme 7 illustrates one particular application of the reactivity-gated concept described above to achieve controlled release of a "releasable agent" or other reactant. In this example, the releasable agent is a dienophile, namely an alkene.



Scheme 7

The butadiene precursor (series 2) undergoes thermally induced condensation reactions with alkenes to generate photoresponsive hexatrienes (series 2o). These ring-open isomers can be transformed into their ring-closed counterparts (series 2c) when irradiated with UV light. The ring-closed isomers are thermally stable and cannot undergo the thermal back reaction. The light effectively "locks" the thermal reaction. The reverse photochemical reaction can be induced with visible light. This "unlocks" the system and allows for the spontaneous thermal release of the alkene. This embodiment relies on the fact that the ring-open form of the hexatriene is unstable and the condensation reaction is reversible. The thermally unstable compound spontaneously fragments to liberate the alkene or other releasable agent(s).

[00039] The structure of the "locked" forms of the molecule can be synthetically modified so that different wavelengths of light can trigger the release of different compounds providing a means to selectively release one compound in the presence of others. Also, the differences in optical and electronic properties of the "locked" and released forms of the compounds provides a means to monitor the spacial and temporal release of the compounds. This will be useful for the delivery of releasable agents such as therapeutics, biochemical effectors, polymer precursors, biorelevant molecules and chemical reagents for photolithography and for locking thermally reversible polymerization processes.

[00040] This embodiment of the invention offers a universal photorelease approach where the electronic properties of the chromophore (**series 2c**) can be fine-tuned by tailoring the photoresponsive scaffold without negatively affecting the performance of the system. This embodiment is adaptable to many chemistries and environments, and can be applied to many different substrates and many different situations. It also offers a means to selectively and sequentially release different species using light of different wavelengths. Because the "locked" compounds absorb long-wavelength light, cellular damage is minimized. The molecular system is also easily derivatized using synthetic methods that are tolerant to a wide range of chemistries. This controlled photorelease approach may be useful for drug delivery and photodynamic therapy applications.

[00041] The technology extends far beyond the discharge of molecules selectively with a high degree of temporal and spatial control. Because the two derivatives (**series 2**) and (**series 2c**) exhibit a wide range of properties unique to their structures, the technology offers a means to "release and report" to quantify the extent and location of discharge by monitoring an optical or electronic read-out signal including, but not limited to, color, refractive index, luminescence and redox chemistry.

Applications

[00042] In one embodiment the invention involves the reversible connection and insulation of two functional groups at each end of a conjugated pathway and the use of reactivity-gated switching to provide an additional means to regulate this concept. The result is that any application that benefits from this connection/disconnection mechanism will potentially be impacted. This includes, but is not limited to, optoelectronics (optical filters, data storage), electro-optics (waveguides), health sciences (drug release and photodynamic therapy) and chemical reactivity (catalysis and reagents).

[00043] As indicated above, linear conjugation within D–π–A systems often results in significant polarization of the molecule and is the basis for numerous useful and important materials properties such as refractive index, non-linear optical properties and the absorption/reflection of light. Photoregulating these properties will impact many optoelectronic, electro-optic and photonic applications such as waveguides, reflectors, filters and dyes.

[00044] In one embodiment of the invention the hexatriene compound may bear a phenol group at the position labeled R_4 (Scheme 1). This embodiment structurally resembles tyrphostins, which have shown potential as protein tyrosine kinase (PTK) inhibitors. The ability of kinases to influence the growth and progression of proliferative conditions has made them attractive targets for new chemotherapeutics, including small molecule inhibitor drugs that specifically target kinases known to be deregulated in cancers. Acting as signal blockers, tyrphostins are a promising class of inhibitors that has proven to be effective at inhibiting the growth of tumor cell lines and in vivo tumors. The tyrphostins share a common dehydrated tyrosine sub-structure as shown by the hydroxy-benzylidene-malonodinitriles (e.g. AG17) and hydroxy-benzylidene-cyclopentendione (e.g. KIH and TX) series. As will be apparent to a person skilled in the art, the functional groups of the compounds of the invention may be tailored to mimic, inhibit or otherwise regulate biological active molecules.

[00045] Other important examples include those that have acidic, basic or nucleophilic groups as the 'A' or 'D' groups. In these cases, the connection through the linear π–system results in the increase or decrease (depending on the example) of the reactivity of the particular group. Photo- or electrocyclization reverses the response. This provides a versatile means to photo- or electromodulate chemical reactivity on command and has the potential to significantly influence catalysis and chemical processing.

[00046] The concept of reactivity-gated photochromism and electrochromism has the potential to significantly impact numerous applications. It can be applied to sensing and dosiometry applications, taking advantage of the wide range of output signals offered by the systems (e.g. absorption, emission, redox). It can be applied to controlled release

systems (e.g. drug delivery) and to the tuning of the mechanical properties of polymers. The compounds described here provide access to novel methods to prepare photochromic and electrochromic compounds. They also provide access to novel monomers for the preparation of functional polymers.

EXAMPLES

[00047] The following examples are intended to illustrate embodiments of the invention and are not intended to be construed in a limiting manner.

Experimental

[00048] **Materials.** All solvents used for synthesis and UV–VIS absorption spectroscopy were dried by passing them through steel columns containing activated alumina under nitrogen using an MBraun solvent purification system. Solvents for NMR analysis were purchased from Cambridge Isotope Laboratories and used as received. Column chromatography was performed using silica gel 60 (230-400 mesh) from Silicycle Inc. and solvents purchased from Aldrich that were used as received. The starting materials, 2-fluoro-1-(2'-methyl-5'-phenylthien-3'-yl)hexafluorocyclopentene (**1**) [7]. 1,2-bis(2,5-dimethyl-3-thienyl)ethanedione (**23**) [8] and 1,4-butanebis(triphenylphosphonium) dibromide [9], 1,2-bis(5'-phenyl-2'-methylthieny-3'-yl)cyclopentene (**28**) [10], 1,2-bis(5'-chloro-2'-methylthieny-3'-yl)cyclopentene (**29**) [11] and diethyl dicyanofumarate [12] were prepared as described in the literature. All other reagents and starting materials were purchased from Aldrich.

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7 Peters, A.; Vitols, C.; McDonald, R.; Branda, N. R. *Org. Lett.* **2003**, *5*, 1183.

8 Ivanov, S. N.; Litchitskii, B. V.; Martynkin, A. Y.; Krayushkin, M. M. *Chem. Heterocycl. Comp.* **2001**, *37*, 85.

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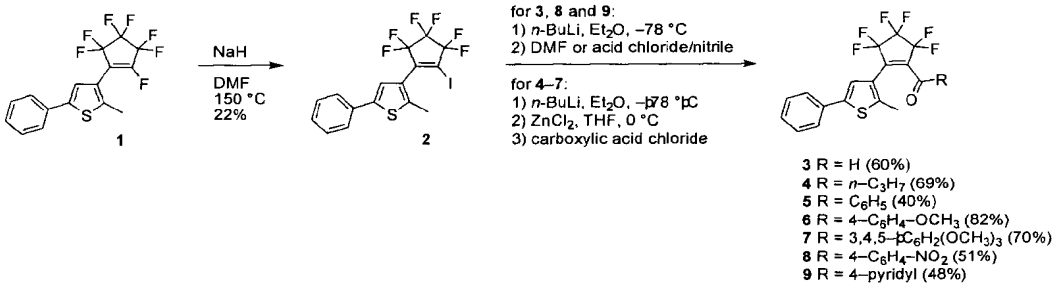
11 Lucas, L. N. van Esch, J. H.; Kellogg, R. M.; Feringa, B. L. *Chem. Commun.* **1998**, 2313.

[00049] **Instrumentation.** ^{1}H NMR characterizations were performed on a Varian INOVA 500 working at 499.770 MHz or a Bruker AMX 400 instrument working at 400.103 MHz. ^{13}C NMR characterizations were performed on a Bruker AMX 400 instrument working at 100.610 MHz. ^{19}F NMR characterizations were performed on a Varian Inova 500 instrument. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane using the residual solvent peak as a reference standard. ^{19}F NMR spectra were referenced against $BrCH_2BrCF_2$ (–52.1 ppm). Coupling constants (J) are reported in hertz. FT-IR measurements were performed using a Nicolet Nexus 670 instrument. UV–VIS absorption spectroscopy was performed using a Varian Cary 300 Bio spectrophotometer. Exact mass measurements were done using a Kratos Concept-H instrument with perfluorokerosene as the standard.

[00050] **Photochemistry.** All ring-closing reactions were carried out using the light source from a lamp used for visualizing TLC plates at 313 nm or 365 nm(Spectroline E-series, 470 W/cm^2). The ring-opening reactions were carried out using the light of a 300-W halogen photo optic source passed through appropriate cutoff filters to eliminate higher energy light. The selective ring-opening reactions were carried out using the light source (75 W xenon lamp) from a PTI QM-2000-4 scanning spectrofluorimeter.

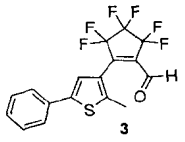
Scheme 8



[00051] **Synthesis of iodoperfluorocyclopentene 2.** A solution of heptafluorocyclopentene **1** (680 mg, 1.84 mmol) and anhydrous sodium iodide (560 mg,

12 Ireland, C. J.; Jones, K.; Pizey, J. S.; Johnson, S. *Synth. Commun.* **1976**, *6*, 185.

3.52 mmol) in anhydrous DMF (4 mL) was placed in a nitrogen flushed 10 mL pyrex tube equipped with a magnetic stir bar. The tube was sealed and the solution was heated to 150 °C in an oil bath for 6 h and then stirred at room temperature overnight. The solution was diluted with diethyl ether (100 mL) and washed with water (4 × 15 mL). The organic layer was dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification by column chromatography (SiO_2, hexanes) afforded 189 mg (22 %) of the compound **2** as a white solid. Mp = 74 °C; ^{1}H NMR ($CDCl_3$): δ = 2.46 (s, 3H), 7.10 (s, 1H), 7.31 (m, 1H), 7.39 (m, 2H), 7.55 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 15.3, 122.2, 125.9, 128.2, 129.2, 133.5, 140.6, 142.8; MS (CI): 475 (M^+).

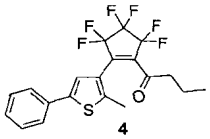


3

[00052] **Synthesis of aldehyde 3.** A solution of iodide **2** (200 mg, 0.42 mmol) in anhydrous Et_2O (25 mL) was cooled in an acetone/dry-ice bath to –78 °C and treated with *n*-BuLi (170 µL, 2.5 M in hexane, 0.42 mmol) in one portion via a syringe. The resulting yellow solution was stirred for 15 min at –78 °C before anhydrous DMF (97 µl, 1.26 mmol) was added. After stirring for another 10 min, the reaction was quenched with saturated aqueous NH_4Cl and the cooling bath was removed. The two layers were allowed to warm to room temperature, separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexane/ethyl acetate 6:1) afforded 95 mg of compound **3** (60%) as a yellow solid. Mp = 89–91 °C; ^{1}H NMR (CD_2Cl_2): δ = 2.50 (s, 3H), 7.31 (s, 1H), 7.37 (m, 1H), 7.44 (m, 2H), 7.60 (m, 2H), 9.77 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.7, 122.7, 126.0, 128.7, 129.3, 132.8, 143.8, 145.6, 184.8; MS (CI): 377 (M^+).

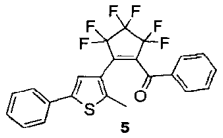
[00053] **Synthesis of ketones 4–7.** In a 25 mL three-necked flask, compound **2** (200 mg, 0.42 mmol) was dissolved in anhydrous Et_2O (8 mL). The solution was cooled to –78 °C under a nitrogen atmosphere and treated with *n*-BuLi (186 µL, 2.5 M in hexane, 0.46 mmol) in one portion. After stirring for 15 min at this temperature, a solution of anhydrous zinc chloride (64 mg, 0.46 mmol) in anhydrous THF (0.8 mL) was added

drop-wise. The acetone/dry-ice bath was exchanged with an ice bath and after stirring for further 30 min, all solvents were removed under reduced pressure. The resulting residue was dissolved in anhydrous THF (0.5 mL), cooled to 0 °C and treated with the appropriate carboxylic acid chloride (0.5 mmol), followed by a catalyst solution (0.5 mL) prepared from $[Pd(PPh_3)_2]Cl_2$ (21 mg) and *i*-Bu_2AlH (36 mL, 1.5 M in toluene) dissolved in anhydrous benzene (1 mL). Stirring was continued for 30 min at which time the ice-bath was removed and the dark red solution was stirred overnight at room temperature. After quenching with 1N aqueous HCl, the mixture was extracted with hexane (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried with brine and $MgSO_4$, filtered and the solvents were evaporated under reduced pressure.



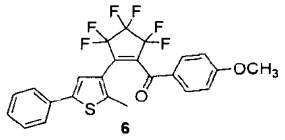
4

[00054] (**4**) Prepared from *n*-butanoyl chloride and purified by column chromatography (SiO_2, 10:1 hexane/ethyl acetate gradient) as a yellow solid in 69% yield (121 mg). Mp = 67–68 °C; ^{1}H NMR ($CDCl_3$): δ = 0.85 (t, J = 7.0 Hz, 3H), 1.59 (tq, J = 7.0, 7.0 Hz, 2H), 2.34 (s, 3H), 2.50 (t, J = 7.0 Hz, 2H), 7.15 (s, 1H), 7.32 (m, 1H), 7.40 (m, 2H), 7.55 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 13.6, 14.6, 16.8, 44.7, 122.4, 124.2, 125.9, 128.4, 129.3, 133.2, 142.5, 143.1, 196.2; MS (CI): 419 (M^+).



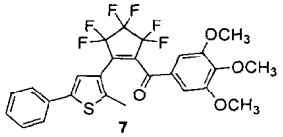
5

[00055] (**5**) Prepared from benzoyl chloride and purified by column chromatography (SiO_2, 10:1 hexane/ethyl acetate) as a yellow solid in 40% yield (78 mg). Mp = 70–73 °C; ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3H), 7.11 (s, 1H), 7.29 (m, 1H), 7.36 (m, 4H), 7.42 (m, 2H), 7.53 (m, 1H), 7.73 (m, 2H); MS (CI): 453 (M^+).



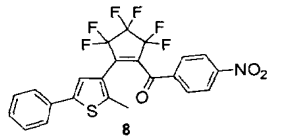
6

[00056] (**6**) Prepared from 4-methoxybenzoyl chloride and purified by column chromatography (SiO_2, hexane/ethyl acetate 5:1) and recrystallization from hexane as a yellow solid in 82% yield (87 mg). Mp = 87–89 °C; ^{1}H NMR ($CDCl_3$): δ = 2.31 (s, 3H), 3.81 (s, 3H), 6.84 (m, 2H), 7.13 (s, 1H), 7.28 (m, 1H), 7.35 (m, 2H), 7.44 (m, 2H), 7.73 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.8, 55.8, 114.4, 122.6, 124.4, 125.8, 128.1, 128.2, 129.2, 132.0, 133.3, 142.8, 143.0, 165.2, 186.9; MS (CI): 483 (M^+).



7

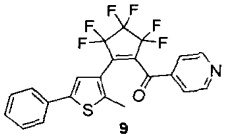
[00057] (**7**) Prepared from compound **2** (250 mg, 0.53 mmol), *n*-BuLi (240 μL, 2.5 M in hexane, 0.59 mmol), zinc chloride (80 mg, 0.58 mmol) and 3,4,5-trimethoxybenzoyl chloride (0.5 mmol). The product was purified by column chromatography (SiO_2, 5:1 hexane/ethyl acetate) as a yellow solid in 70% yield (200 mg). Mp = 111–112 °C; ^{1}H NMR ($CDCl_3$): δ = 2.33 (s, 3H), 3.82 (s, 6H), 3.88 (s, 3H), 7.02 (s, 2H), 7.14 (s, 1H), 7.30 (m, 1H), 7.36 (m, 2H), 7.43 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.8, 56.4, 61.2, 107.1, 122.4, 125.7,128.4, 129.2, 129.8, 133.0, 143.1, 143.2, 144.7, 153.3, 187.2; MS (CI): 543 (M^+).



8

[00058] **Synthesis of ketone 8.** A solution of iodide **2** (200 mg, 0.42 mmol) in anhydrous Et_2O (8 mL) was cooled to –78 °C under a nitrogen atmosphere and treated with *n*-BuLi (1.86 mL, 2.5 M in hexane, 0.46 mmol) in one portion. After stirring for 15 min at this temperature, 4-nitrobenzoyl chloride (78 mg, 0.42 mmol) was added. The resulting green solution was stirred at –78 °C for 1 h, the acetone/dry-ice bath was removed and the solution was allowed to warm to room temperature, during which time a colour changed from yellow to reddish brown. The solvent was removed under reduced pressure and the resulting residue was transferred to a silica column (SiO_2, hexanes/ethyl acetate 11:1). Purification by column chromatography afforded 107 mg (51%) of ketone **8** as a yellow solid. Mp = 95–97 °C; ^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3H), 7.11 (s, 1H), 7.31

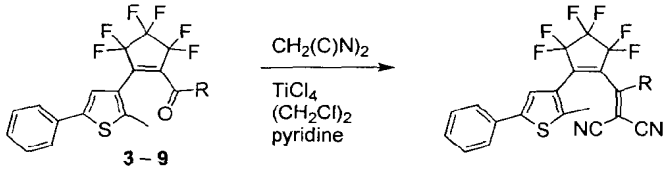
(m, 1H), 7.37 (m, 2H), 7.40 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.7,122.0, 124.2, 125.9, 128.6, 129.3, 130.1, 132.7, 139.3, 143.7, 144.0, 151.2, 187.7; MS (CI): 498 (M^+).



9

[00059] **Synthesis of ketone 9.** A solution of iodide **2** (200 mg, 0.42 mmol) was dissolved in anhydrous Et_2O (8 mL). The solution was cooled to –78 °C under a nitrogen atmosphere and treated with *n*-BuLi (1.86 mL, 2.5 M in hexane, 0.46 mmol) in one portion. After stirring for 15 min at this temperature, 4-cyanopyridine (44 mg, 0.42 mmol) was added. The orange solution was stirred at –78 °C for further 20 min, at which time the acetone/dry-ice bath was exchanged with an ice-bath. Stirring was continued for an additional 15 min before the brown solution was acidified with 6 N HCl to pH 1. After 1 h, the pH was adjusted to 10 by addition of solid KOH while cooling with ice. The mixture was extracted with ethyl acetate and the extracts were dried over $MgSO_4$. The solvent was removed in vacuum. The resulting dark brown oil was transferred to a column (SiO_2, hexanes/ethyl acetate 5:1) and purified by column chromatography to afford 91 mg (48%) of ketone **9** as a yellow solid. ^1H NMR ($CDCl_3$): δ = 2.25 (s, 3H), 7.10 (s, 1H), 7.31 (m, 1H), 7.37 (m, 2H), 7.42 (m, 2H), 7.49 (br s, 2H), 8.72 (br s, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.7,122.1, 124.3, 126.0, 128.7, 129.3, 132.7, 140.9, 143.8, 144.0, 151.1, 188.8; MS (CI): 454 (M^+).

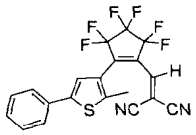
Scheme 9



10 R = H (93%)
11 R = *n*–C_3H_7 (83%)
12 R = C_6H_5 (74%)
13 R = 4–C_6H_4–OCH_3 (36%)
14 R = 3,4,5–$\beta C_6H_2(OCH_3)_3$ (26%)
15 R = 4–C_6H_4–NO_2 (62%)
16 R = 4–pyridyl (83%)

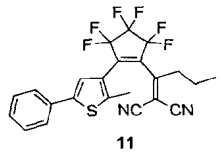
[00060] **Synthesis of compounds 10–15.** A solution of aldehyde **3** or the appropriate ketone **4–9** (0.1 mmol) and malonodinitrile (16.5 mg, 0.25 mmol) in

anhydrous dichloroethane (5 mL) was cooled in an ice bath to 0 °C under nitrogen atmosphere and treated with $TiCl_4$ (0.1 ml, 0.91 mmol) drop-wise. After stirring for 5 min, pyridine (0.2 mL) was carefully added over 20 min. The purple reaction mixture was allowed to warm to room temperature and subsequently heated at reflux for 5–10 min during which time a white precipitate formed and the colour changed to pale brown. After cooling to room temperature, the solvents were evaporated under reduced pressure. The solid residue was dissolved in 15% aqueous HCl (10 mL), the solution was extracted with $CHCl_3$ (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. Purification of the crude product affords compounds **10–15**.



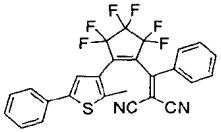
10

[00061] (**10**) Prepared from aldehyde **3** in 93% yield (40 mg) as an orange solid. ^{1}H-NMR spectroscopy indicated the product was pure enough to use without further purification. Mp = 102–104 °C; ^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 3H), 7.18, 7.21 (2s, 2 × 1H), 7.36 (m, 1H), 7.42 (m, 2H), 7.55 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 15.3, 92.6, 109.9, 112.6, 122.3, 124.4, 126.2, 129.0, 129.4, 132.5, 144.8, 145.3; ^{19}F NMR ($CDCl_3$): δ = –108.55, –113.49, –133.51; MS (CI): 425 (M^+); Anal Calcd. C 56.61, H 2.38, N 6.60; Found: C 56.32, H 2.50, N 6.77.



11

[00062] (**11**) Prepared from ketone **4** and purified by column chromatography (SiO_2, hexane/ethyl acetate 10:1) on a short silica plug (2.5 cm Ø × 4 cm) as an orange-yellow oil in 83% yield (39 mg). ^{1}H NMR ($CDCl_3$): δ = 1.03 (t, J = 7.0 Hz, 3H), 1.66 (tq, J = 7.0, 7.0 Hz, 2H), 2.45 (s, 3H), 2.70 (m, 2H), 7.03 (s, 1H), 7.34 (m, 1H), 7.41 (m, 2H), 7.52 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 15.2, 21.7, 38.3, 93.0, 110.7, 123.2, 122.8, 126.0, 128.6, 129.4, 132.9, 142.6, 143.8, 167.4; ^{19}F NMR ($CDCl_3$): δ = –110.02, –113.37, –134.36; MS (CI): 467 (M^+); Anal Calcd. C 59.22, H 3.46, N 6.01; Found: C 59.08, H 3.63, N 6.20.

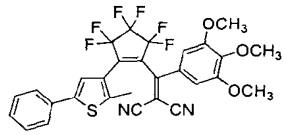


12

[00063] (**12**) Prepared from ketone **5** and purified by column chromatography (SiO_2, hexane/ethyl acetate 10:1) as an yellow solid in 74% (39 mg). Mp = 110–111 °C; ^1H NMR ($CDCl_3$): δ = 2.43 (s, 3H), 6.88 (s, 1H), 7.32 (m, 1H), 7.37 (m. 2H), 7.41 (m, 2H), 7.55 (m, 2H, ar C*H*), 7.63 (m, 3H, ar C*H*); ^{13}C NMR ($CDCl_3$): δ = 15.1, 88.8, 111.9, 112.1, 122.5, 123.3, 125.9, 128.5, 129.3, 129.4, 129.8, 132.1, 132.9, 134.2, 143.2, 143.5, 161.2; ^{19}F NMR ($CDCl_3$): δ = –109.53, –113.52, –134.72; MS (CI): 501 (M^+); Anal Calcd. C 62.40, H 2.82, N 5.60; Found: C 62.16, H 3.01, N 5.30.

13

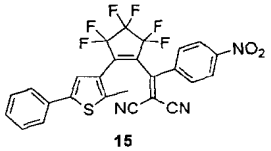
[00064] (**13**) Prepared from ketone **6** and purified by column chromatography (SiO_2, hexane/ethyl acetate 10:1) as an orange oil in 36% yield (19 mg). ^1H NMR ($CDCl_3$): δ = 2.45 (s, 3H), 3.89 (s, 3H), 6.87 (s, 1H), 7.02 (m, 2H), 7.29 (m, 1H), 7.36 (m, 4H), 7.70 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 15.3, 56.1, 84.5, 112.6, 113.0, 114.8, 115.3, 122.7, 123.2, 124.0, 125.9, 128.4, 129.3, 129.9, 132.2, 133.0, 143.1, 143.2, 159.5, 164.9; ^{19}F NMR ($CDCl_3$): δ = –110.13, –113.37, –134.79; MS (CI): 531 (M^+); Anal Calcd. C 61.13, H 3.04, N 5.28; Found: C 61.34, H 3.02, N 5.10.



14

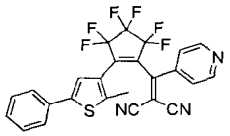
[00065] (**14**) Prepared from ketone **7** (0.25 mmol), malanodinitrile (0.68 mmol), $TiCl_4$ (2.28 mmol) and pyridine (0.5 mL). The product was purified by column chromatography (SiO_2, 4:1 hexane/acetone) on a long silica column (2.5 cm Ø × 80cm) as an orange oil in 26% yield (39 mg). ^1H NMR ($CDCl_3$): δ = 2.46 (s, 3H), 3.85 (s, 6H), 3.96 (s, 3H), 6.84 (s, 1H), 6.92 (s, 2H), 7.32 (m, 1H), 7.37 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 159.9, 153.5, 143.9, 143.4, 143.1, 132.8, 129.4, 128.6, 126.4, 125.9,

123.2, 122.7, 112.8, 112.2, 107.4, 86.1, 61.5, 56.6, 32.9, 29.9, 15.2 (21 of 24 carbons found).



15

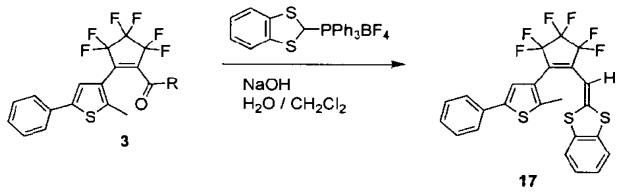
[00066] (**15**) Prepared from ketone **8** and purified by column chromatography (SiO_2, hexane/ethyl acetate 10:1) as a red solid in 62% yield (34 mg). ^1H NMR ($CDCl_3$): $\delta = 2.46$ (s, 3H), 6.78 (s, 1H), 7.33 (m, 1H), 7.36 (m, 2H), 7.68 (d, $J = 9.0$ Hz, 2H), 8.34 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 15.2$, 66.1, 92.4, 111.0, 111.2, 122.0, 123.3, 124.2, 124.8, 125.9, 128.9, 129.4, 130.2, 132.4, 137.8, 143.8, 144.3, 150.3, 159.0; ^{19}F NMR ($CDCl_3$): $\delta = -108.82, -113.64, -134.56$; MS (CI): 546 ($M^+$); Anal Calcd. C 57.25, H 2.40, N 7.70; Found: C 57.21, H 2.60, N 7.50.



16

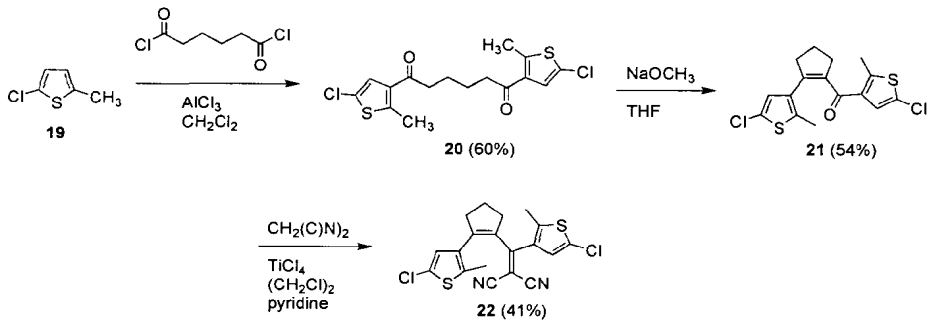
[00067] (**16**) A solution of ketone **9** (0.1 mmol) and malonodinitrile (16.5 mg, 0.25 mmol) in anhydrous dichloroethane (5 mL) was cooled in an ice bath to 0 °C under nitrogen atmosphere and treated drop-wise with $TiCl_4$ (0.1 ml, 0.91 mmol). After stirring for 5 min, pyridine (0.2 mL) was carefully added over a 20 min period. The purple reaction mixture was allowed to warm to room temperature and subsequently heated at reflux for 60 min. After cooling to room temperature, the solvents were evaporated under reduced pressure. The solid brown residue was dissolved in H_2O (10 mL) and the solution was extracted with chloroform (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexanes/ethyl acetate 5:2) afforded **16** in 83% yield (42 mg). ^1H NMR ($CDCl_3$): $\delta = 2.43$ (s, 3H), 6.78 (s, 1H), 7.32–7.38 (m, 7H), 8.86 (br s, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 15.2$, 92.7, 111.0, 111.2, 122.0, 126.0, 128.8, 129.4, 132.5, 139.6, 143.6, 144.2, 151.3, 159.0; ^{19}F NMR ($CDCl_3$): $\delta = -108.80, -113.59, -134.62$; MS (CI): 502 ($M^+$); EA: Anal Calcd. C 59.88, H 2.61, N 8.38; Found: C 59.71, H 2.86, N 8.13.

Scheme 10



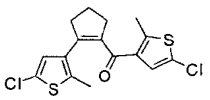
[00068] **Synthesis of compound 17.** In a 10 mL flask, a suspension of (22.5 mg, 0.06 mmol) of aldehyde **3** and 1,3-benzodithiolyl-triphenylphosphonium tetrafluoroborate (30 mg, 0.06 mmol) in CH_2Cl_2 (0.3 mL) was treated with aqueous NaOH (0.3 mL of 50% *w/w*). The mixture was stirred at room temperature for 3 h and then extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with water (3 × 5 mL) and sat. NaCl (1 × 5 mL). After drying over $MgSO_4$ and filtering, the solvent was removed under reduced pressure and the residue purified by column chromatography (SiO_2, hexanes/ethyl acetate 10:1) on a short silica plug (Ø 2.5 cm × 5 cm). The product was isolated as a yellow solid in 72 % yield (22.0 mg). M.p. 49–54 °C; ^{1}H NMR ($CDCl_3$): δ = 2.24 (s, 3H), 6.23 (s, 1H), 7.12–7.18 (m, 3H), 7.29–7.34 (m, 3H), 7.41 (m, 2H), 7.60 (m, 2H); MS (CI): 513 (M^+).

Scheme 11



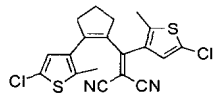
[00069] **Synthesis of diketone 20.** A solution of 2-chloro-5-methylthiophene **19** (4.19 g, 31.1 mmol) and adipoyl chloride (2.3 mL, 15.8 mmol) in anhydrous CH_2Cl_2 (70 mL) was cooled to 0 °C under nitrogen atmosphere using an ice bath. The solution was treated with portions of $AlCl_3$ (5.30 g, 39.7 mmol). The cooling bath was removed and

the solution was allowed to warm at room temperature and was stirred overnight under nitrogen atmosphere. The mixture was poured on an ice (100 g) and aqueous HCl (10 mL) mixture and stirred 1 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with $NaHCO_3$ (3 × 100 mL), then brine (100 mL), dried with $MgSO_4$, filtered and evaporated to dryness under reduced pressure. Purification by recrystallization from hexanes afforded 3.60 g of **20** as a colourless solid. (60%). ^{1}H NMR ($CDCl_3$): δ = 7.16 (s, 2H), 2.80 (m, 4H), 2.65 (s, 6H), 1.74 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 195.3, 147.8, 135.2, 127.0, 125.5, 41.7, 23.7, 16.2.



21

[00070] **Synthesis of ketone 21.** A solution of diketone **20** (1.50 g, 4.0 mmol) in anhydrous THF (150 mL) under nitrogen atmosphere was treated with sodium methoxide (1.10 g, 20 mmol). The solution was heated to reflux for 12 h while kept in the dark and under nitrogen atmosphere. The mixture was allowed to cool to room temperature and treated with aqueous NH_4Cl (150 mL) and stirred for 15 min. The aqueous layer was removed and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered and evaporated to dryness under reduced pressure. Purification by column chromatography through silica (1:19 EtOAc:hexanes) afforded a pale yellow oil that was crystallized from Et_2O (777 mg, 54%). ^{1}H NMR ($CDCl_3$): δ = 6.60 (s, 1H), 6.51 (s, 1H), 2.86 (t, J = 7.5 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H), 2.54 (s, 3H), 2.12 (s, 3H), 2.03 (q, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ = 190.5, 145.7, 145.2, 141.4, 136.0, 135.1, 133.6, 128.1, 126.5, 126.3, 124.6, 40.0, 35.3, 22.6, 15.2, 14.3.

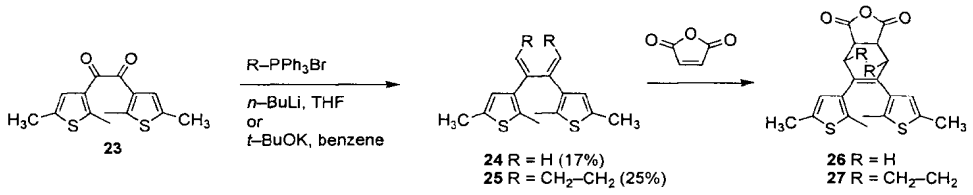


22

[00071] **Synthesis of compound 22.** A solution of ketone **21** (65 mg, 0.18 mmol) and malonodinitrile (30 mg, 0.45 mmol) in anhydrous dichloroethane (10 mL) under nitrogen atmosphere was cooled to 0 °C using an ice bath. The solution was treated drop-wise with $TiCl_4$ (0.18 mL, 1.6 mmol). After stirring for 5 min, pyridine (0.35 mL) was

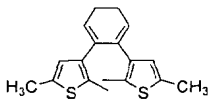
carefully added over 20 min. The reaction mixture was allowed to warm at room temperature and subsequently heated to reflux for 7 min during which time a white precipitate was formed. After cooling at room temperature, the solvent was evaporated under reduced pressure. The remaining solid was dissolved in 15% aqueous HCl (20 mL) and $CHCl_3$ (10 mL) was added. The water layer was separated and extracted with chloroform (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography through silica (1:19 EtOAc:hexanes) afforded 30 mg (41%) of **22** as a yellow oil. ^1H NMR ($CDCl_3$): $\delta = 6.54$ (s, 1H), 6.25 (s, 1H), 2.97 (t, $J = 7.4$ Hz, 2H), 2.77 (t, $J = 7.4$ Hz, 2H), 2.33 (s, 3H), 2.20 (s, 3H), 2.12 (q, $J = 7.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$) $\delta = 165.3$, 153.2, 142.3, 137.8, 135.3, 133.0, 132.6, 127.9, 126.7, 126.4, 126.0, 113.7, 113.2, 40.0, 36.8, 24.0, 15.5, 14.4.

Scheme 12



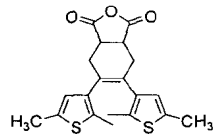
[00072] **Synthesis of 2,3-bis(2,5-dimethyl-3-thienyl)-1,3-butadiene (24).** *n*-Butyllithium (0.64 ml of a 2.5 M solution in hexanes, 1.6 mmol) was added drop-wise to a cooled (0 °C) suspension of methyltriphenylphosphonium bromide (568 mg, 1.6 mmol) in THF (50 mL). After the addition was completed, the ice bath was removed and the reaction mixture was allowed to slowly warm to room temperature, at which point it was stirred for 45 min. The resulting yellow solution was cooled to –78 °C and treated drop-wise with a solution of 1,2-bis(2,5-dimethyl-3-thienyl)ethanedione **23** (89 mg, 0.32 mmol) in THF (10 mL). The reaction mixture was stirred at –78 °C for 30 min, the dry ice/acetone bath was removed and the reaction was allowed to warm to room temperature. After stirring overnight, the reaction was quenched by the addition of water (50 mL) and extracted with Et_2O (3 × 50 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography through silica (1:9 EtOAc:hexanes) to yield 15 mg (17%) of diene **24** as a white solid. Mp = 43–44 °C;

^{1}H NMR ($CDCl_3$); δ = 6.52 (s, 2H), 5.13 (d, J = 3.4 Hz, 2H), 5.09 (d, J = 3.4 Hz, 2H), 2.40 (s, 6H), 2.31 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 144.5, 137.7, 135.1, 133.0, 127.9, 118.5, 15.4, 14.1; MS (EI): m/z = 274 (M^+).



25

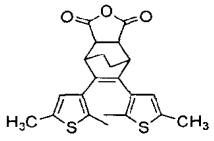
[00073] **Synthesis of 3,4-bis(2,5-dimethyl-3-thienyl)cyclohexadiene (25).** Potassium *t*-butoxide (163 mg, 1.45 mmol) was added to a suspension of 1,4-butanebis(triphenylphosphonium) dibromide (537 mg, 0.725 mmol) in benzene (50 mL). The reaction was stirred for 45 min at room temperature. The resulting orange solution was heated to reflux and treated drop-wise with a solution of 1,2-bis(2,5-dimethyl-3-thienyl)ethanedione **23** (202 mg, 0.72 mmol) in benzene (25 mL). The reaction mixture was stirred at reflux for 20 min, at which point the heating mantle was removed and the reaction was allowed to cool to room temperature. The reaction was quenched by the addition of water (50 mL) and extracted with Et_2O (3 × 50 mL). The organic extracts were combined, washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was purified by column chromatography through silica (1:9 EtOAc:hexanes) to yield 55 mg (25%) of **25** as a white solid. Mp = 55–57 °C. ^{1}H NMR ($CDCl_3$): δ = 6.13 (s, 2H), 5.88 (m, 2H), 2.26 (m, 10H), 2.14 (s, 6H); ^{13}C NMR ($CDCl_3$) δ = 137.8, 134.4, 133.9, 131.6, 127.4, 126.7, 22.7, 15.1, 14.0. MS (EI): m/z = 300 (M^+).



26

[00074] **Synthesis of cyclohexene 26:** A solid mixture of 2,3-bis(2,5-dimethyl-3-thienyl)-1,3-butadiene **24** (6.8 mg, 0.03 mmol) and maleic anhydride (4.9 mg, 0.05 mmol) was heated to 70 °C using an oil bath. Upon the complete melting of both solids, a pale pink solid formed. The cyclohexene product (**26**) was purified by column chromatography through silica (1:4 EtOAc:hexanes) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 6.32 (s, 2H), 3.53 (d, J = 2.4 Hz, 2H), 2.96 (d, J = 15.1 Hz, 2H), 2.65 (dd, J = 15.1, 2.4

Hz, 2H), 2.33 (s, 6H), 1.73 (s, 6H).



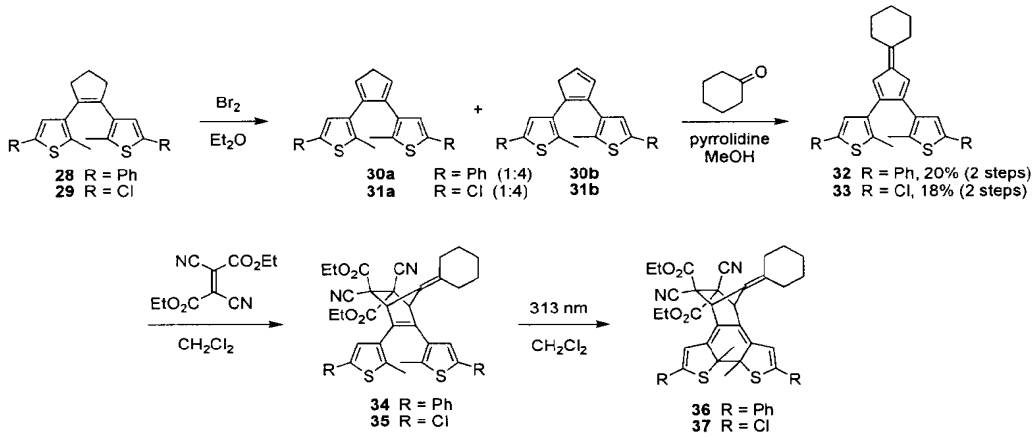
27

[00075] **Synthesis of bicyclic product 27 – Procedure 1.** 3,4-Bis(2,5-dimethyl-3-thienyl)cyclohexadiene **25** (5 mg) and maleic anhydride (5 mg) were mixed in a 10 mL round bottom flask. The mixture turned from colorless to yellow within the first few seconds. After standing for 1 h at room temperature, product **27** was purified by column chromatography through silica (1:4 EtOAc:hexanes) as a white solid. The efficiency of the reaction was greatly improved when melting both components by heating to 70 °C in an oil bath. ^{1}H NMR ($CDCl_3$): δ = 6.45 (s, 2H), 3.43 (m, 2H), 3.26 (m, 2H), 2.35 (s, 6H), 1.65 (s, 6H), 1.54 (m, 4H). MS (EI): m/z = 398 (M^+).

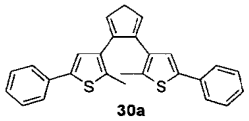
[00076] **Procedure 2.** 3,4-Bis(2,5-dimethyl-3-thienyl)cyclohexadiene **25** (1 mg) and maleic anhydride (1 mg) were dissolved in acetone-d_6 (1 mL) in an NMR tube and heated to 65 °C in a water bath. The reaction went to completion after 7 days and no side products were observed by ^{1}H NMR spectroscopy. ^{1}H NMR (acetone-d_6): δ = 6.55 (s, 2H), 3.54 (m, 2H), 3.35 (m, 2H), 2.35 (s, 6H), 1.89 (dm, J = 7.4 Hz, 2H), 1.65 (dm, J = 7.4 Hz, 2H), 1.65 (s, 6H).

[00077] **Procedure 3.** 3,4-Bis(2,5-dimethyl-3-thienyl)cyclohexadiene **25** (20 mg, 6.8×10^{-5} mol) and maleic anhydride (6.5 mg, 6.8×10^{-5} mol) were dissolved in acetone-d_6 (0.75 mL) in an NMR tube and heated at 65 °C in a water bath. The reaction went to completion after 5 days and no side products were observed by ^{1}H NMR spectroscopy. Thin layer chromatography and ^{13}C NMR spectroscopy showed the presence of trace amount of impurities. The product was purified by column chromatography through silica (1:4 EtOAc:hexanes). Mp = >185 °C (decomposition); ^{1}H NMR (acetone-d_6): δ = 6.55 (s, 2H), 3.54 (m, 2H), 3.35 (m, 2H), 2.35 (s, 6H), 1.89 (dm, J = 7.4 Hz, 2H), 1.65 (m, 2H), 1.65 (s, 6H); ^{13}C NMR (acetone-d_6): δ = 175.2, 137.8, 137.3, 136.9, 133.9, 127.2, 46.8, 40.7, 25.2, 15.9, 14.8; MS (EI): m/z = 398 (M^+).

Scheme 13

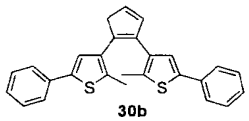


[00078] **Synthesis of cyclopentadiene isomers 30a and 30b.** A solution of 1,2-bis(5'-phenyl-2'-methylthieny-3'-yl)cyclopentene (**28**) (280 mg, 0.73 mmol) in anhydrous Et_2O (50 mL) was cooled to –40 °C under nitrogen atmosphere using an acetone/dry ice bath. The solution was kept in the dark while it was treated with bromine (36 μL, 0.73 mmol) in one portion using a syringe. The cooling bath was removed, the reaction was allowed to warm to room temperature and was stirred for 1 h. The reaction was quenched with water (10 mL) and stirred for 10 min. The aqueous layer was separated and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (10 mL), then brine (10 mL), dried with Na_2SO_4, filtered and evaporated to dryness under reduced pressure. Purification by column chromatography through silica (18:1 hexanes:EtOAc containing 1% Et_3N) afforded a colorless oil containing the isomers **30a** and **30b** in a 1:4 ratio.



30a

[00079] (**30a**) ^{1}H NMR ($CDCl_3$): δ = 7.42 (d, J = 7.7 Hz, 4H), 7.29 (t, J = 7.7 Hz, 4H), 7.21 (t, J = 7.7 Hz, 2H), 6.87 (s, 2H), 6.48 (t, J = 1.5 Hz, 2H), 3.28 (t, J = 1.5 Hz, 2H), 2.27 (s, 6H).

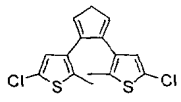


30b

[00080] (**30b**) ^{1}H NMR ($CDCl_3$): δ = 7.50 (d, J = 7.6 Hz, 4H), 7.33 (t, J = 7.6 Hz,

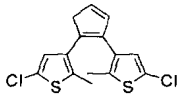
4H), 7.22 (t, J = 7.6 Hz, 2H), 7.09 (s, 1H), 7.08 (s, 1H), 6.71 (dt, J = 5.5, 1.5 Hz, 1H), 6.53 (dt, J = 5.5, 1.5 Hz, 1H), 3.50 (t, J = 1.5 Hz, 2H), 2.12 (s, 3H), 2.03 (s, 3H).

[00081] **Synthesis of cyclopentadiene isomers 31a and 31b.** A solution of 1,2-bis(5'-chloro-2'-methylthieny-3'-yl)cyclopentene **29** (203 mg, 0.61 mmol) in anhydrous Et_2O (25 mL) was cooled to –40 °C under nitrogen atmosphere using an acetone/dry ice bath. The solution was kept in the dark while it was treated with bromine (31 μL, 0.61 mmol) in one portion using a syringe. The cooling bath was removed, the reaction was allowed to warm to room temperature and was stirred for 1 h. The reaction was quenched with water (10 mL) and stirred for 10 min. The aqueous layer was separated and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, filtered and evaporated to dryness under reduced pressure. Purification by column chromatography through silica (19:1 hexanes:EtOAc containing 1% Et_3N) afforded 94 mg (47 %) of a colorless oil containing the isomers **31a** and **31b** in a 1:4 ratio.



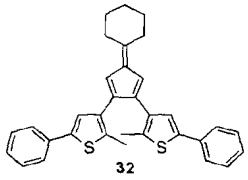
31a

[00082] (**31a**) ^{1}H NMR ($CDCl_3$): δ = 6.41 (s, 2H), 6.38 (t, J = 1.8 Hz, 2H), 3.22 (t, J = 1.8 Hz, 2H), 2.16 (s, 6H). ^{1}H NMR (acetone-D_6) δ 6.50 (t, J = 1.8 Hz, 2H), 6.48 (s, 2H), 3.28 (t, J = 1.8 Hz, 2H), 2.20 (s, 6H).



31b

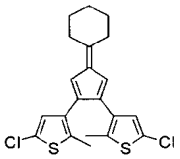
[00083] (**31b**) ^{1}H NMR ($CDCl_3$): δ = 6.63 (s, 1H), 6.62 (s, 1H), 6.57 (dt, J = 1.5, 5.2 Hz, 1H), 6.48 (dt, J = 1.5, 5.2 Hz, 1H), 3.36 (t, J = 1.5 Hz, 2H), 2.02 (s, 3H), 1.92 (s, 3H); ^{1}H NMR (acetone-D_6): δ = 6.84 (s, 1H), 6.73 (s, 1H), 6.65 (dt, J = 1.5, 5.4 Hz, 1H), 6.55 (dt, J = 1.5, 5.4 Hz, 1H), 3.47 (t, J = 1.5 Hz, 2H), 2.06 (s, 3H), 1.94 (s, 3H): ^{13}C NMR (acetone-D_6): δ = 139.0, 138.6, 137.1, 136.2, 136.1, 136.0, 135.1, 134.7, 129.8, 129.3, 126.7, 126.4, 47.4, 15.2, 15.1.



32

[00084] **One-pot synthesis of 2,3-bis(2'-phenyl-5'-methylthieny-3'-yl)-6,6-pentamethylenefulvene (32).** A solution of 1,2-bis(5'-phenyl-2'-methylthieny-3'-yl)cyclopentene (**28**) (1.00 g, 2.40 mmol) in anhydrous Et_2O (100 mL) was cooled to –40 °C under nitrogen atmosphere using an acetone/dry ice bath. The solution was kept in the dark while it was treated with bromine (125 µL, 2.4 mmol) in one portion using a syringe. The cooling bath was removed, the reaction was allowed to warm to room temperature and was stirred in the dark under nitrogen atmosphere. The reaction was monitored by TLC (hexanes). After approximately 1 h all starting materials had been consumed and water (10 mL) was added to quench any unreacted bromine. The reaction was stirred for 10 min when the aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered and evaporated to dryness under reduced pressure. The crude product was dissolved in methanol (50 mL) and was deoxygenated by bubbling nitrogen gas through it for 30 min. It was then treated with deoxygenated cyclohexanone (0.50 mL, 4.8 mmol) and deoxygenated pyrrolidine (410 µL, 4.8 mmol). The reaction was stirred at room temperature for 12 h in the dark. The methanol was evaporated in vacuo to yield a brown solid. The crude mixture was dissolved in Et_2O (100 mL), washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated under reduced

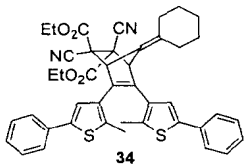
pressure to yield a brown solid. Purification by column chromatography using silica (hexanes) afforded 242 mg (20%) of **32** as a yellow solid. Mp. 163 °C; ^{1}H NMR (CD_2Cl_2): δ = 7.46 (d, J = 7.8 Hz, 4H), 7.30 (t, J = 7.8 Hz, 4H), 7.20 (t, J = 7.8 Hz, 2H) 6.93 (s, 2H), 6.66 (s, 2H), 2.74 (m, 4H), 2.32 (s, 6H), 1.82 (m, 4H), 1.74 (m, 2H); ^{13}C NMR (CD_2Cl_2): δ = 160.5, 141.9, 140.9, 140.1, 137.4, 137.0, 136.4, 130.6, 128.8, 127.4, 127.2, 121.0, 35.5, 30.8, 28.4, 16.1; MS (CI) m/z = 491 (M+1), 493 (M+3); MS (EI) m/z = 492 (M+2); EA (calc.) C, 80.77; H, 6.16; (exp.) C, 80.39; H, 6.35.



33

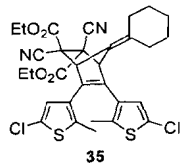
[00085] **One-pot synthesis of 2,3-bis(2'-chloro-5'-methylthieny-3'-yl)-6,6-pentamethylenefulvene (33).** A solution of 1,2-bis(5'-chloro-2'-methylthieny-3'-yl)cyclopentene (**29**) (1.00 g, 3.04 mmol) in anhydrous Et_2O (75 ml) was cooled to –40 °C under nitrogen atmosphere using an acetone/dry ice bath. The solution was kept in the dark while it was treated with bromine (160 µL, 3.0 mmol) in one portion using a syringe. The cooling bath was removed, the reaction was allowed to warm to room temperature and was stirred in the dark under nitrogen atmosphere. The reaction was monitored by TLC (hexanes). After approximately 2 h, all starting materials had been consumed and water (10 mL) was added to quench any unreacted bromine. The reaction was stirred for 10 min when the aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (10 mL), $NaHCO_3$ saturated aqueous solution (10 mL), and brine (10 mL), dried with $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The crude product was dissolved in methanol (50 mL) and was deoxygenated by bubbling nitrogen gas through it for 30 min. It was then treated with deoxygenated cyclohexanone (1.56 mL, 15.2 mmol) and deoxygenated pyrrolidine (1.27 mL, 15.2 mmol). The reaction was stirred at room temperature for 14 h in the dark. The methanol was evaporated in vacuo to yield a brown solid. The crude mixture was dissolved in Et_2O (100 mL), washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$ and evaporated under reduced pressure to yield a brown solid. Purification by column chromatography using silica (hexanes) afforded 222 mg (18%) of **33** as a yellow

solid. Mp. 144–146 °C;^{1}H NMR (CD_2Cl_2): δ = 6.57 (s, 2H), 6.47 (s, 2H), 2.70 (m, 4H), 2.21 (s, 6H), 1.78 (m, 4H), 1.72 (m, 2H); ^{13}C NMR (CD_2Cl_2): δ = 159.6, 138.4, 137.5, 133.5, 133.4, 127.6, 124.2, 119.4, 33.3, 28.6, 26.1, 13.6; MS (EI) m/z = 406 (M+); EA (calc.) C, 61.91; H, 4.95; (exp.) C, 61.81; H 5.08.



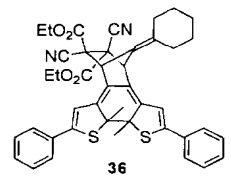
34

[00086] **Synthesis of bicyclic compound 34.** A solution of fulvene **32** (5.0 mg, 0.01 mmol) in CD_2Cl_2 (0.75 mL) was treated with diethyldicyanofumerate (9.4 mg, 0.05 mmol) in one portion in an NMR tube. The reaction was monitored by ^{1}H NMR spectroscopy and reached equilibrium within 20 minutes when 45% of product was obtained. The equilibrium constant (K_{eq}) was calculated to be 16 M^{-1}. ^{1}H NMR (CD_2Cl_2): δ = 7.56 (m, 4H), 7.50 (s, 1H), 7.39 (m, 6H), 7.16 (m, 1H), 4.40-4.00 (m, 6H), 2.7-2.6 (m, 2H), 2.3-2.0 (m, 2H), 1.97 (s, 3H), 1.92 (s, 3H), 1.63 (m, 6H), 1.16 (m, 6H).



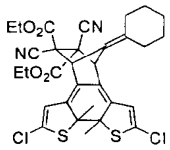
35

[00087] **Synthesis of bicyclic compound 35.** A solution of the fulvene **33** (5.5 mg, 0.01 mmol) in CD_2Cl_2 (0.75 mL) at room temperature was treated with diethyldicyanofumerate (11 mg, 0.05 mmol) in one portion in an NMR tube. The reaction was monitored by ^{1}H NMR spectroscopy and reached equilibrium within 20 minutes when 43% of product was obtained. The equilibrium constant (K_{eq}) was calculated to be 13 M^{-1}. ^{1}H NMR (CD_2Cl_2): δ = 7.02 (s, 1H), 6.77 (s, 1H), 4.30 (s, 2H), 4.3-4.2 (m, 2H), 4.1-4.0 (m, 2H), 2.5-2.0 (m, 4H), 1.84 (s, 3H), 1.81 (s, 3H), 1.7-1.4 (m, 6H), 1.42 (t, 3H), 1.23 (t, 3H).



36

[00088] **Synthesis of ring-closed compound 36.** A solution of fulvene **32** (50 mg, 0.1 mmol) in CH_2Cl_2 (15 mL) was treated with diethyldicyanofumerate (68 mg, 0.3 mmol). The solution was kept in the dark while it was stirred for 15 min. The solution was then irradiated with 313-nm light for 15 min. Further irradiation resulted in the formation of a significant amount of an uncharacterized side product. The solution was evaporated under vacuum and in the dark to yield a red/purple solid. Purification by column chromatography in the dark using silica (hexanes:EtOAc 18:1) afforded **36** as a mixture of two stereoisomers which were not separated. In order to avoid ring-opening of **36**, the compound must be kept in absolute darkness. Stereoisomer 1 (major): ^{1}H NMR (CD_2Cl_2): δ = 7.54 (m, 4H)*, 7.39 (m, 6H)*, 6.57 (s, 1H), 6.51 (s, 1H), 4.40-4.20 (m, 6H)*, 2.5-2.1 (m, 6H)*, 2.05 (s, 3H)*, 1.98 (s, 3H)*, 1.7-1.5 (m, 4H), 1.39 (m, 6H)*. Stereoisomer 2 (minor): ^{1}H NMR (CD_2Cl_2): δ = 7.54 (m, 4H)*, 7.39 (m, 6H)*, 6.55 (s, 1H), 6.52 (s, 1H), 4.40-4.20 (m, 6H)*, 2.5-2.1 (m, 6H)*, 2.05 (s, 3H)*, 1.98 (s, 3H)*, 1.7-1.5 (m, 4H), 1.39 (m, 6H)*. (*Observed as overlapping peaks of stereoisomers.)



37

[00089] **Synthesis of ring-closed compound 37.** A solution of fulvene **33** (56 mg, 0.1 mmol) in CH_2Cl_2 (7.5 mL) was treated with diethyldicyanofumarate (116 mg, 0.5 mmol). The solution was kept in the dark while it was stirred for 1 h. The solution was then irradiated with 313-nm light for 8 minutes. Further irradiation resulted in the formation of a significant amount of an uncharacterized side product. The solution was evaporated under vacuum and in the dark to yield a yellow/orange solid. Purification by column chromatography in the dark using silica (hexanes:EtOAc 19:1) afforded **37** as a mixture of two stereoisomers. Recrystalization with hexanes afforded a solid enriched with the major stereoisomer and a solute enriched with the minor stereoisomer. In order to avoid ring-opening of **37**, the compound must be kept in absolute darkness. Stereoisomer 1 (major): ^{1}H NMR (CD_2Cl_2): δ = 6.10 (s, 1H), 6.06 (s, 1H), 4.40-4.20 (m, 4H)*, 4.17 (s, 1H), 4.12 (s, 1H)*, 2.40-2.25 (m, 4H)*, 2.15-2.10 (m, 2H)*, 2.02 (s, 3H)*, 1.94 (s, 3H)*, 1.7-1.5 (m, 4H)*, 1.39 (m, 6H)*. Stereoisomer 2 (minor): ^{1}H NMR

(CD_2Cl_2): δ = 6.08 (s, 1H), 6.05 (s, 1H), 4.40-4.20 (m, 4H)*, 4.12 (s, 1H)*, 4.06 (s, 1H), 2.40-2.25 (m, 4H)*, 2.15-2.10 (m, 2H)*, 2.02 (s, 3H)*, 1.94 (s, 3H)*, 1.7-1.5 (m, 4H)*, 1.39 (m, 6H)*. (*Observed as overlapping peaks of stereoisomers.)

Photocyclization Reactions of Compounds 10–17

[00090] Scheme 14 below shows reversible photocyclization of compounds **10 – 17** at different wavelengths of light, namely 365 nm light for conversion from the ring-open to the ring-closed form, and 490 nm light for conversion from the ring-closed and ring-open form.

10 – 17

Scheme 14

Characterization of compounds 10-17

[00091] Figure 1 are graphs showing changes in the UV-VIS absorption spectra of solutions of compounds **10–17** when irradiated with 365-nm light (313 nm for **12**). The solvent, concentrations and total irradiation times for each compound are provided in the figure. Figure 2 are graphs showing the modulated absorptions of the ring-open isomers (□) and the ring-closed isomers (●) during alternating UV and VIS irradiations. The irradiation wavelengths and times for each compound are provided in the figure. One UV and one VIS irradiation occurs in each cycle. The Figure 1 and 2 graphs demonstrate that compounds **10–17** are photoactive., i.e. there is a change in the absorption spectra of each compound when they are irradiated and there is little degradation when the compounds are subjected to several ring-closing/ring-opening cycles.

Characterization of compound 24

[00092] Figure 3A is a graph showing changes in the UV–VIS absorption spectra when an acetonitrile solution (2×10^{-5} M) of **26** is irradiated with 313-nm light for a total of 45 seconds (solid lines) and 254-nm light for 45 seconds (dashed line). Figure 3B is a graph showing changes in the UV–VIS absorption spectra when an acetonitrile solution (2×10^{-5} M) of **27** is irradiated with 313-nm light for a total of 45 seconds (solid lines) and 254-nm light for 45 seconds (dashed line). The experimental data shown in Figures 3A and 3B confirm that compounds 24 and 25 are photoactive.

Characterization of the photostationary state containing **25** and **27**.

[00093] A $CDCl_3$ solution of **25** (1×10^{-3} M) was irradiated with 313-nm light for 1-minute periods and ^1H NMR spectra were obtained after each irradiation. The photostationary state (containing 31% of the ring-closed isomer 27) was obtained after a total of 4 minutes of irradiation.

(**27**) ^1H NMR ($CDCl_3$): δ = 7.72 (s, 1H), 7.50 (s, 1H), 3.23 (m, 1H), 3.22 (m, 1H), 3.12 (m, 1H), 3.11 (m, 1H), 2.08 (s, 6H), 1.89 (s, 3H), 1.84 (s, 3H), 1.54 (m, 4H).

[00094] Figure 4A is a picture showing the color change that occurs when a DMSO solution of diene **25** and excess maleic anhydride are mixed and exposed to 313-nm light (right spot). The left spot is a sample containing only the diene **25** that has been simultaneously irradiated. Cyclohexadiene **25** (1 mg) was added to a saturated solution of maleic anhydride in DMSO (0.5 mL) and a small amount of DMSO was added (~0.5 mL) to dissolve the remaining solid. A solution containing only the cyclohexadiene was also prepared (1 mg in 1 mL). One drop of each solution was deposited on a microscope slide and placed on a heating stage at 35 °C for 30 minutes. After this heating period, the samples were simultaneously irradiated for 30 seconds with 313-nm light. The sample containing maleic anhydride and the cyclohexadiene turned yellow. The other did not. The same behaviour was observed when the solution of maleic anhydride and cyclohexadiene and the control solution were kept at room temperature for 14 hours. Figure 4B shows the same sample of diene **25** and maleic anhydride after bleaching with greater than 415-nm light. These

experiments illustrate the gated photochromism, where the thermal Diels-Alder reaction must occur before the compounds can undergo photoinduced ring-closing.

Characterization of Compounds 32 - 37

[00095] Figure 5 are graphs showing insignificant changes in the UV-VIS absorption spectra when CH_2Cl_2 solutions of compounds **32** and **33** are irradiated with UV light. In the case of **32**, the light source was changed to > 490 nm after 60 seconds. These graphs demonstrate the photostability of compounds **32** and **33**.

[00096] Figure 6 is a graph showing changes in the UV–VIS absorption spectra when a CH_2Cl_2 solution (2.5×10^{-5} M) of the product obtained from the thermal reaction of fulvene **32** and maleic anhydride when the product is irradiated with 313-nm light for a total of 60 seconds. These data confirm that compound **34** is photoactive.

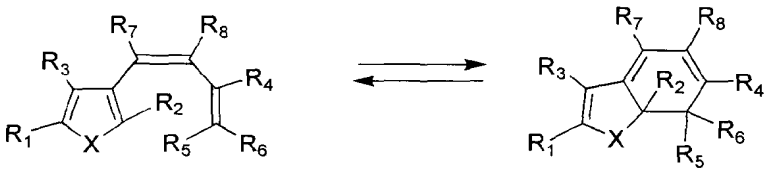
[00097] Figure 7 are UV-VIS absorption spectra: (a) UV–VIS absorption spectra of a CH_2Cl_2 solution (3.4×10^{-5} M) of the ring-closed isomer **36** and a 1:1 mixture of **32** and diethyl dicyanofumarate obtained after the irradiation of **36** with light of wavelengths greater than 490 nm. (b) UV–VIS absorption spectra of a CH_2Cl_2 solution (3.4×10^{-5} M) of the ring-closed isomer **37** and a 1:1 mixture of **33** and diethyl dicyanofumarate obtained after the irradiation of **37** with light of wavelengths greater than 434 nm. (c) The UV–VIS absorption spectrum of a 1:1 mixture (in CH_2Cl_2) of the ring-closed compounds **36** and **37** before (dark grey) and after irradiation with 430-nm light (light grey) to selectively ring-open **37**. (d) The UV–VIS absorption spectrum of a 1:1 mixture (in CH_2Cl_2) of the ring-closed compounds **36** and **37** before (dark grey) and after irradiation with 557-nm light (light grey) to selectively ring-open **36**. (e) The UV–VIS absorption spectrum of a 1:1 mixture (in CH_2Cl_2) of the ring-closed compounds **36** and **37** before (dark grey) and after irradiation with light greater than 434 nm (light grey) to ring open both compound. These data confirm that the release compounds can be selectively released from the thermally stable compounds **36** and **37**.

[00098] Figure 8 are partial ^{1}H NMR (500 MHz, CD_2Cl_2) spectra showing the peaks corresponding to the aromatic protons in (a) fulvene **32**, (b) a 1:1 mixture of **32** and diethyl dicyanofumarate measured when the equilibrium with **34** has been reached, (c) the isolated mixture of ring-closed stereoisomers **36** and (d) a solution of **36** that has been periodically irradiated with greater than 490 nm light showing the disappearance of the ring-closed compounds **36** and the appearance of fulvene **32**. The partial ^{1}H NMR spectra of (e) a 1:1 mixture of **36** and **37** before irradiation (f) after irradiating with 430-nm light to partially ring-open compound **37**, (g) after irradiating the same sample with greater than 557-nm light to partially ring-open compound **36** and (h) after irradiating the same sample with greater than 434-nm light to fully ring-open both compounds. These data confirm that the release compounds can be selectively released from the thermally stable compounds **36** and **37**.

[00099] While a number of exemplary aspects and embodiments have been discussed above, those of skill in the art will recognize certain modifications, permutations, additions and sub-combinations thereof. It is therefore intended that the following appended claims and claims hereafter introduced are interpreted to include all such modifications, permutations, additions and sub-combinations as are within their true spirit and scope.

WHAT IS CLAIMED IS:

1. A compound reversibly convertible between a first ring-open isomeric form represented by the formula I(o) and a second ring-closed isomeric form represented by I(c)



I(o) I(c)

wherein X is a heteroatom selected from the group consisting of S, N and O; R_1 is selected from the group consisting of H, a halogen, alkyl, aryl and substituted aryl; R_2 is selected from the group consisting of alkyl, aryl and substituted aryl; R_3 is selected from the group consisting of H and alkyl; R_4 is selected from the group consisting of H, alkyl, aryl, substituted aryl, an electron-donating group, an electron-accepting group, and a constituent of an optionally substituted heterocycle; R_5 is selected from the group consisting of alkyl, aryl, substituted aryl, an electron-donating group and an electron-accepting group; R_6 is selected from the group consisting of alkyl, aryl, substituted aryl, an electron-donating group, an electron-accepting group and a constituent of an optionally substituted heterocycle; and and R_7 and R_8 are each selected from the group consisting of a constituent of a 5 membered ring comprising H or a halogen or an optionally substituted 6 membered ring ;

wherein, when R_4 and R_6 are constituents of a thiophene ring and R_5 is an alkyl, aryl or substituted aryl, then R_7 and R_8 are constituents of an optionally substituted six-membered ring;

and wherein, when R_7 and R_8 are constituents of a 5 membered halogenated ring then R_4 , R_5 and R_6 are independently not an alkyl or aryl.

2. The compound as defined in claim 1, wherein said compound is convertible between said first and second isomeric forms in response to a light stimulus.

3. The compound as defined in claim 1, wherein said compound is convertible between said first and second isomeric forms in response to an electrical stimulus.

4. The compound as defined in claim 2, wherein said compound is converted from said first form to said second form in response to ultraviolet light and is converted from said second form to said first form in response to visible light.

5. The compound as defined in any one of the preceding claims, wherein R_7 and R_8 together comprise a pentene ring.

6. The compound as defined in claim 5, wherein said pentene ring is halogenated.

7. The compound as defined in claim 6, wherein said pentene ring is fluorinated.

8. The compound as defined in any of the preceding claims wherein R_7 and R_8 together comprise an optionally substituted six membered ring.

9. The compound as defined in claim 1, wherein R_4 and R_6 together comprise a heterocycle.

10. The compound as defined in claim 9, wherein said heterocycle is a thiophene ring.

11. The compound as defined in any one of claims 1 – 10, wherein R_4 comprises an electron-donating group and R_5 and R_6 comprise an electron-accepting group.

12. The compound as defined in any one of claims 1 – 10, wherein R_4 comprises an electron-accepting group and R_5 and R_6 comprise an electron-donating group.

13. The compound as defined in claims 11 and 12, wherein said electron-donating group and said electron-accepting group are linearly conjugated in said first ring-open form.

14. The compound as defined in claim 13, wherein said electron-donating group and said electron-accepting group are electrically insulated in said second ring-closed form.

15. The compound as defined in any one of claims 11 – 14, wherein said electron-accepting group is a carbonyl-based functional group.

16. The compound as defined in any one of claims 11 – 14, wherein said electron-accepting group comprises a dicyanoethylene group.

17. The compound as defined in any one of claims 11 – 16, wherein said electron-accepting and electron-donating groups are electronically connected to each other by an alkene in said first ring-open form.

18. The compound as defined in any of the preceding claims wherein said first and second isomeric forms are thermally stable.

19. The compound as defined in any one of claims 1- 17, wherein said first ring-open isomeric form is thermally unstable and said second ring-closed isomeric form is thermally stable.

20. The compound as defined in claim 1, wherein R_4 is selected from the group consisting of *n*-C_3H_7, C_6H_5, 4-C_6H_4-OCH_3, 3,4,5-$C_6H_2(OCH_3)_3$, 4-C_6H_4-NO_2 and 4-pyridyl.

21. A chemical compound comprising:

(a) a charge transfer moiety comprising an electron donor and an electron acceptor; and

(b) a switching moiety reversibly convertible between a first form and a second form in response to a light or an electrical stimulus, wherein said electron donor and electron acceptor are linearly conjugated to permit charge transfer when said switching moiety is in said first form and wherein said electron donor and electron acceptor are electronically insulated to prevent charge transfer when said switching moiety is in said second form.

22. The compound as defined in claim 21, wherein said switching moiety comprises a hexatriene subunit configured in a ring-open configuration in said first form and a ring-closed configuration in said second form.

23. The compound as defined in claim 22, wherein said first and second forms are photoactive.

24. The compound as defined in any one of claims 21 – 23, wherein conversion of said switching moiety between said first form and said second form causes a change in hybridization of at least one carbon atom connecting said electron donor and said electron acceptor.

25. The compound as defined in claim 21, wherein said charge transfer moiety comprises a dicyanoethylene substituent.

26. The compound as defined in claim 21, wherein said compound comprises the structure defined in claim 1.

27. The compound as defined in claims 1 or 26, wherein switching said compound between said first and second forms alters the chemical reactivity of said compound.

28. The compound as defined in claim 21, wherein said compound is thermally stable in said first and second forms.

29. The compound as defined in claim 21, wherein said compound is thermally unstable in said first form and thermally stable in said second form.

30. A method of selectively releasing a releasable agent comprising:

(a) providing a precursor compound;

(b) reacting said precursor compound with said releasable agent to form a carrier compound, wherein said carrier compound comprises a switching moiety reversibly convertible between a first thermally unstable form and a second thermally stable form in response to a light or an electrical stimulus; and

(c) selectively converting said switching moiety between said second form and said first form to cause controlled release of said releasable agent from said carrier compound.

31. The method as defined in claim 30, wherein said releasable agent is a small molecule.

32. The method as defined in claim 30 or 31, wherein said step of selectively converting said switching moiety comprises exposing said carrier compound to a predetermined wavelength of light.

33. The method as defined in any one of claims 30 – 32, wherein said carrier compound is delivered to a target location prior to said step of selectively converting said switching moiety.

34. The method as defined in claim 33, wherein said target location is located *in vivo*.

35. The method as defined in any one of claims 30 – 34, wherein said switching moiety comprises a hexatriene subunit.

36. The method as defined in claim 30, wherein said carrier compound comprises a charge transfer moiety comprising an electron donor and an electron acceptor, wherein said electron donor and acceptor are and electronically conjugated in said first form and electronically insulated in said second form.

37. The method as defined in claim 36, wherein said precursor is a diene and wherein said reacting comprises chemically reacting said diene with said releasable agent.

38. The method as defined in claim 30, wherein said precursor is photochemically inert.

39. The method as defined in claim 31, wherein said small molecule is selected from the group consisting of therapeutic agents, biochemical effectors, polymer precursors and chemical reagents.

40. The method as defined in claim 30, wherein said method comprises:

(a) providing multiple releasable agents;

(b) coupling each of said multiple releasable agents to said carrier compound; and

(c) selectively releasing said multiple releasable agents by sequentially exposing said carrier compound to different wavelength of light, each of said wavelengths corresponding to at least one of said releasable agents.

41. A photoactive conjugate comprising a compound having a switching moiety reversibly convertible between a first thermally unstable form and a second thermally stable form in response to a light or an electrical stimulus and at least one small molecule bound to said compound, wherein said small molecule is releasable from said compound when said switching moiety is switched from said second form to said first form.

42. A method of synthesizing a photoactive hexatriene compound having the structure defined in claim 1, wherein said method comprises:

(a) providing a photochemically inert precursor compound; and

(b) chemically reacting said precursor compound with a reactant to form said photoactive hexatriene compound.

43. The method as defined in claim 42, wherein said step of chemically reacting said precursor and said reactant is reversible.

44. The method as defined in claims 42 or 43, wherein said precursor compound is a diene and wherein said reactant is a dienophile.

45. The method as defined in claim 44, wherein said dienophile is an alkene.

46. The method as defined in claim 42, wherein said chemically reacting is a condensation reaction.

47. The method as defined in claim 42, wherein said chemically reacting is a cycloaddition.

48. The method as defined in claim 42, wherein said precursor comprises a butadiene backbone.

49. The method as defined in claim 42, wherein said precursor is a butadiene derivative.

50. The method as defined in claim 43, wherein said precursor and said reactant are liberated when said chemical reaction is reversed.

51. A method of testing for the presence of a target compound in a sample comprising:

(a) providing a photochemically inert precursor compound;

(b) chemically reacting said precursor compound with said sample; and

(c) detecting whether said chemical reaction produces a photoactive hexatriene reaction product.

52. A precursor useful for preparation of a photoactive hexatriene compound, wherein said precursor is selected from the group consisting of:

(a) an aldehyde or a ketone capable of reacting with an activated methylene in a dehydration or deoxygenation reaction to form said hexatriene compound; and

(b) a diene capable of reacting with a dienophile in a condensation reaction to form said hexatriene compound.

53. The precursor as defined in claim 52, wherein said precursor is photochemically inert.

54. The precursor as defined in claim 52 or 53, wherein said diene is a butadiene.

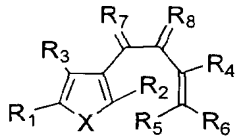
55. The precursor as defined in claim 52 or 53, wherein said diene is a cyclopentadiene.

56. The precursor as defined in claim 55 wherein said cyclopentadiene is non-fluorinated.

57. The precursor as defined in claim 52 or 53, wherein said diene is a cyclohexadiene.

58. The precursor as defined in claim 52 or 53, wherein said diene is a fulvene.

59 The precursor as defined in claim 54, wherein diene is represented by the formula II



II

wherein X is a heteroatom selected from the group consisting of S, N and O; R_1 is selected from the group consisting of H, a halogen, alkyl, aryl and substituted aryl; R_2 is selected from the group consisting of alkyl, aryl and substituted aryl; R_3 is selected from the group consisting of H and alkyl; R_4 is selected from the group consisting of H, alkyl, aryl, substituted aryl, an electron-donating group, an electron-accepting group, and a constituent of an optionally substituted heterocycle; R_5 is selected from the group consisting of alkyl, aryl, substituted aryl, an electron-donating group and an electron-accepting group; R_6 is selected from the group consisting of alkyl, aryl, substituted aryl, an electron-donating group, an electron-accepting group and a constituent of an optionally substituted heterocycle; and R_7 and R_8 are each selected from the group consisting of a constituent of a 5 or and optionally substituted 6 membered ring.

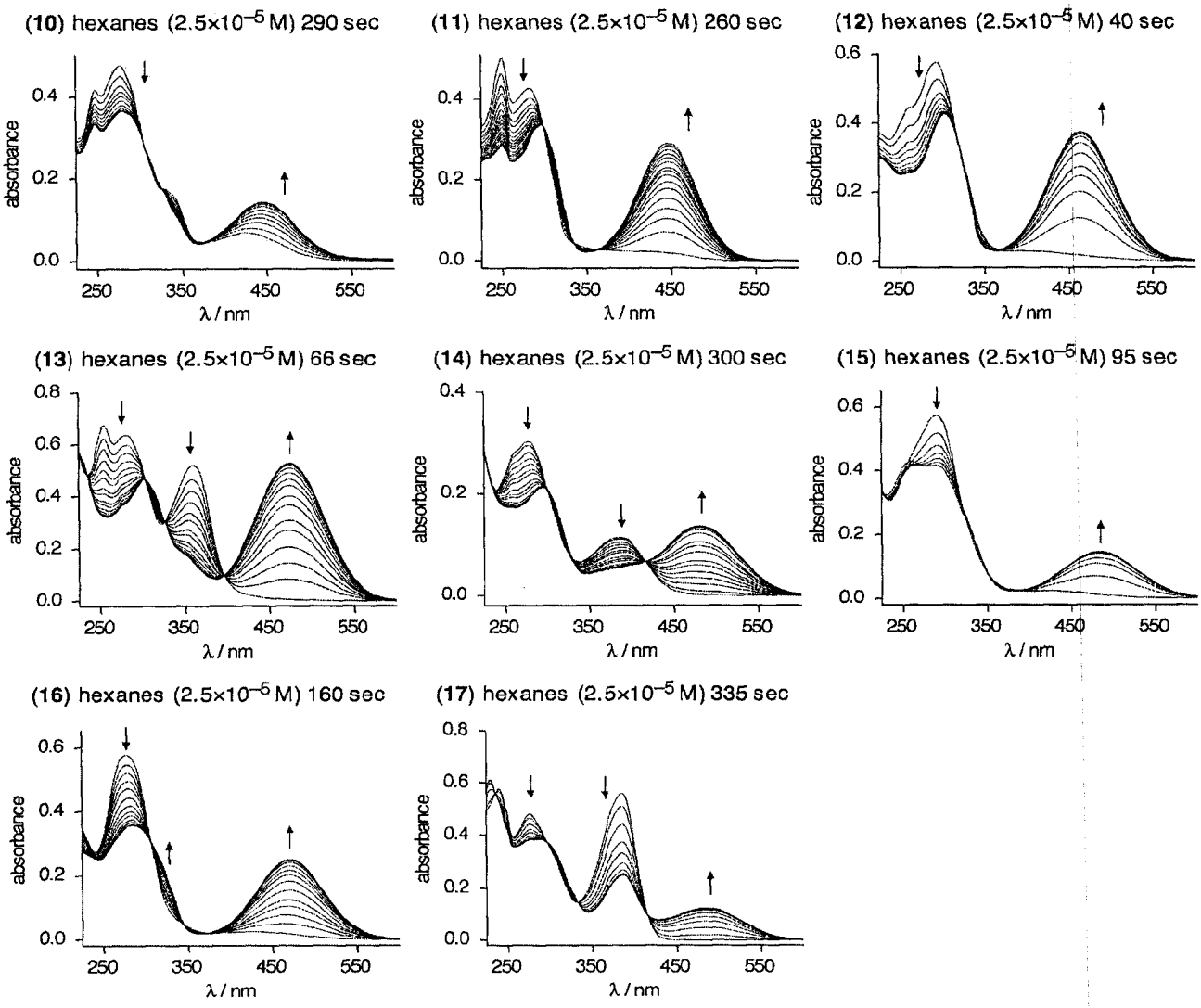

(10) hexanes (2.5x10^{-5} M) 290 sec
(11) hexanes (2.5x10^{-5} M) 260 sec
(12) hexanes (2.5x10^{-5} M) 40 sec
(13) hexanes (2.5x10^{-5} M) 66 sec
(14) hexanes (2.5x10^{-5} M) 300 sec
(15) hexanes (2.5x10^{-5} M) 95 sec
(16) hexanes (2.5x10^{-5} M) 160 sec
(17) hexanes (2.5x10^{-5} M) 335 sec
absorbance
λ / nm

Figure 1

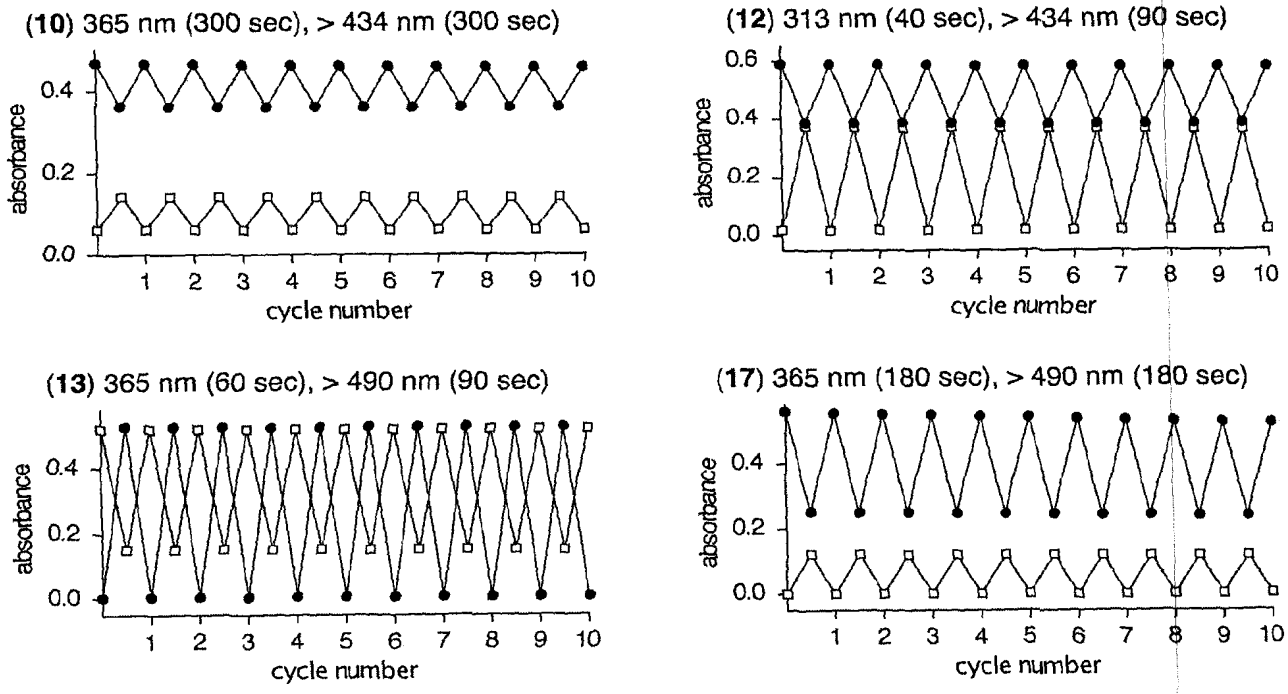

(10) 365 nm (300 sec), > 434 nm (300 sec)
absorbance
0.0
0.2
0.4
1 2 3 4 5 6 7 8 9 10
cycle number
(12) 313 nm (40 sec), > 434 nm (90 sec)
absorbance
0.0
0.2
0.4
0.6
1 2 3 4 5 6 7 8 9 10
cycle number
(13) 365 nm (60 sec), > 490 nm (90 sec)
absorbance
0.0
0.2
0.4
1 2 3 4 5 6 7 8 9 10
cycle number
(17) 365 nm (180 sec), > 490 nm (180 sec)
absorbance
0.0
0.2
0.4
1 2 3 4 5 6 7 8 9 10
cycle number

Figure 2

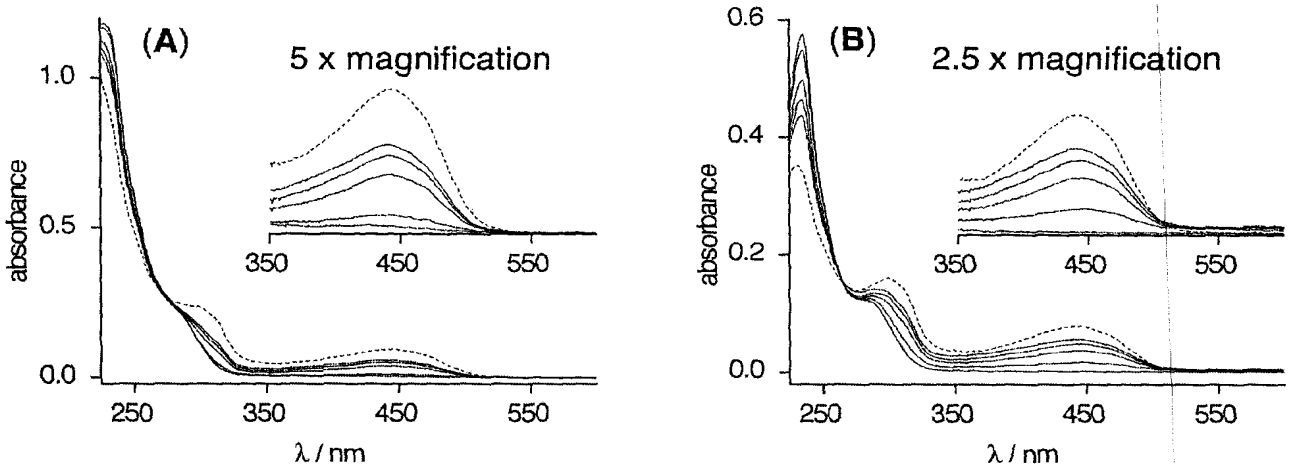


Figure 3

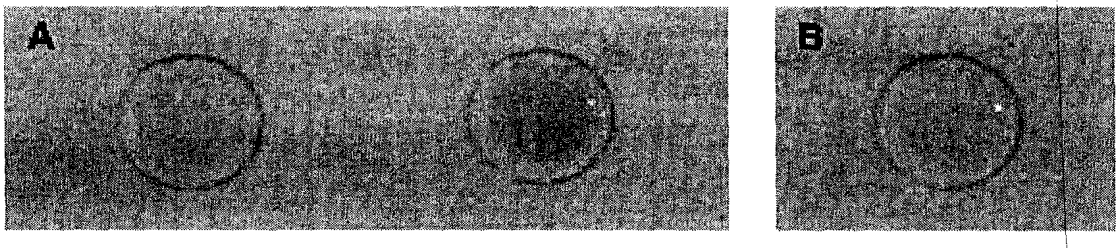


Figure 4

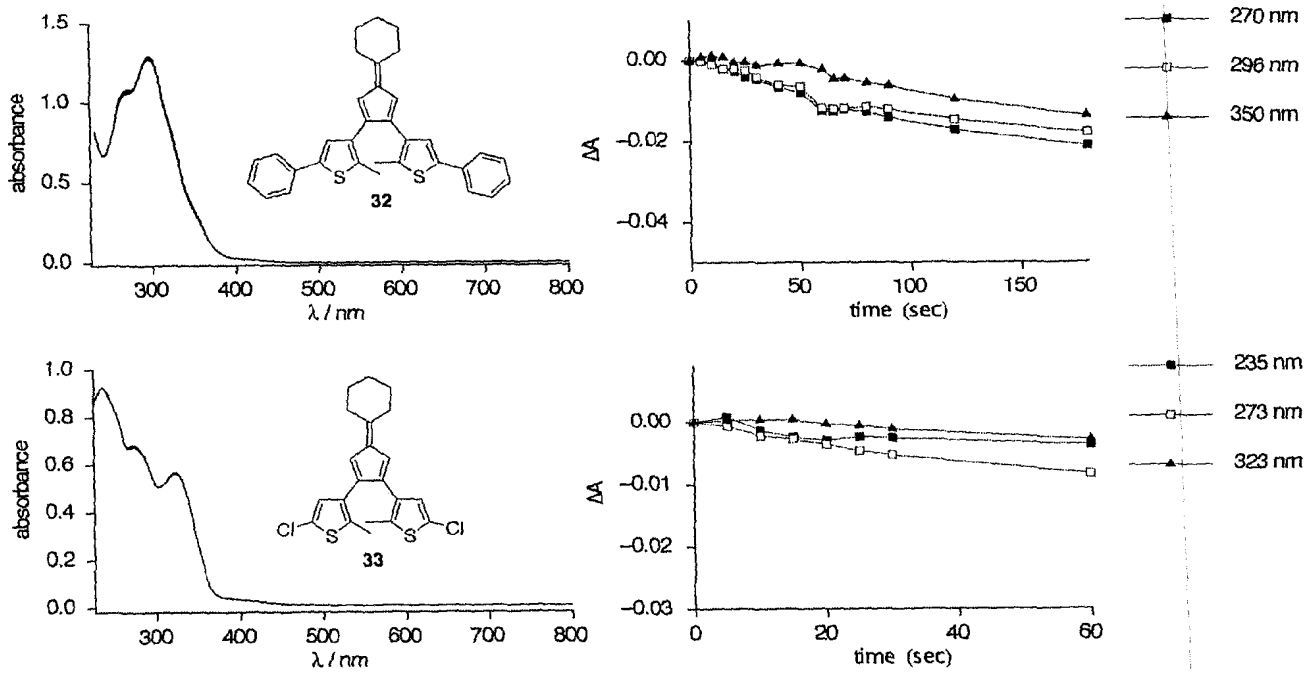

absorbance
λ / nm
32
ΔA
time (sec)
270 nm
296 nm
350 nm
33
235 nm
273 nm
323 nm

Figure 5

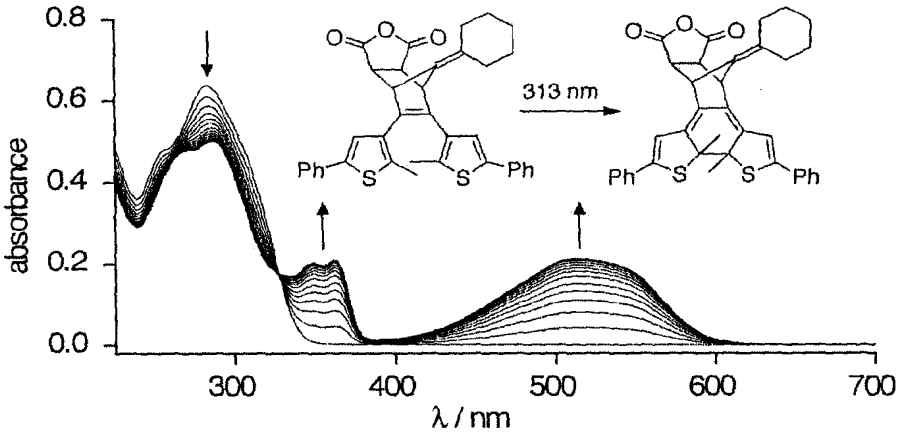


Figure 6

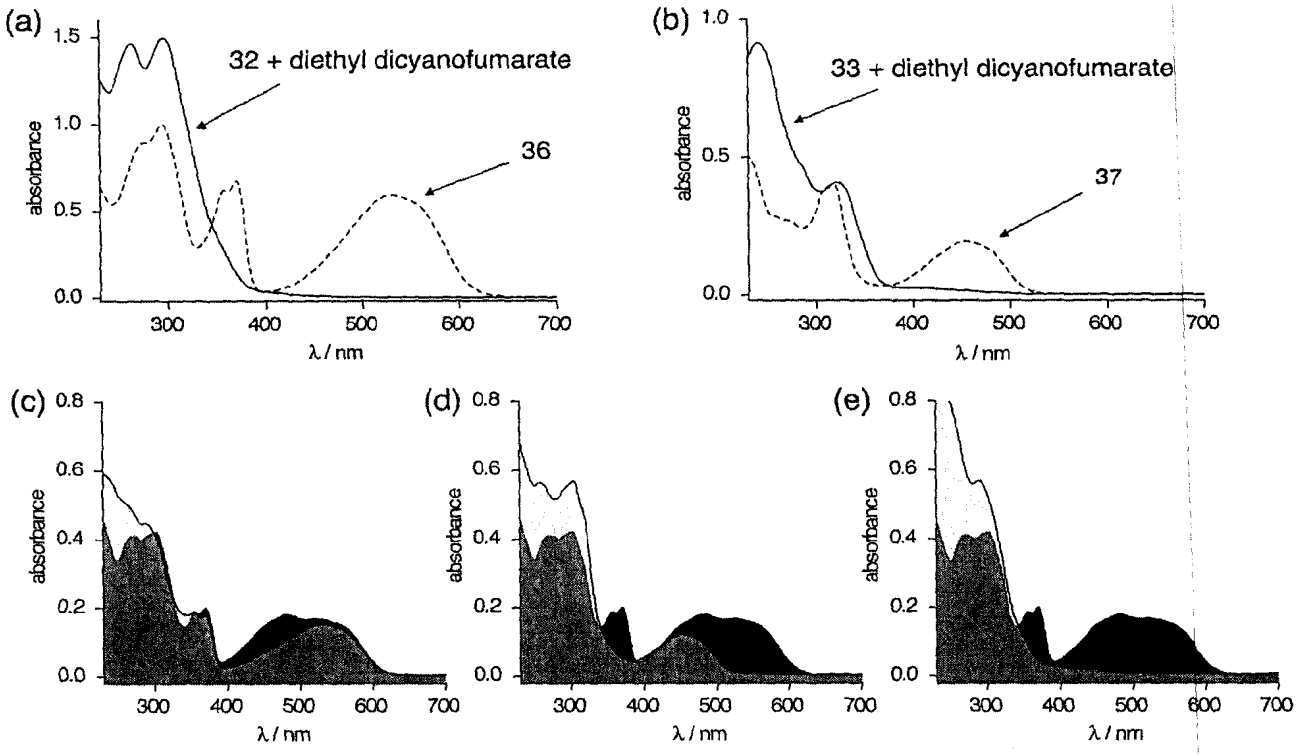


Figure 7

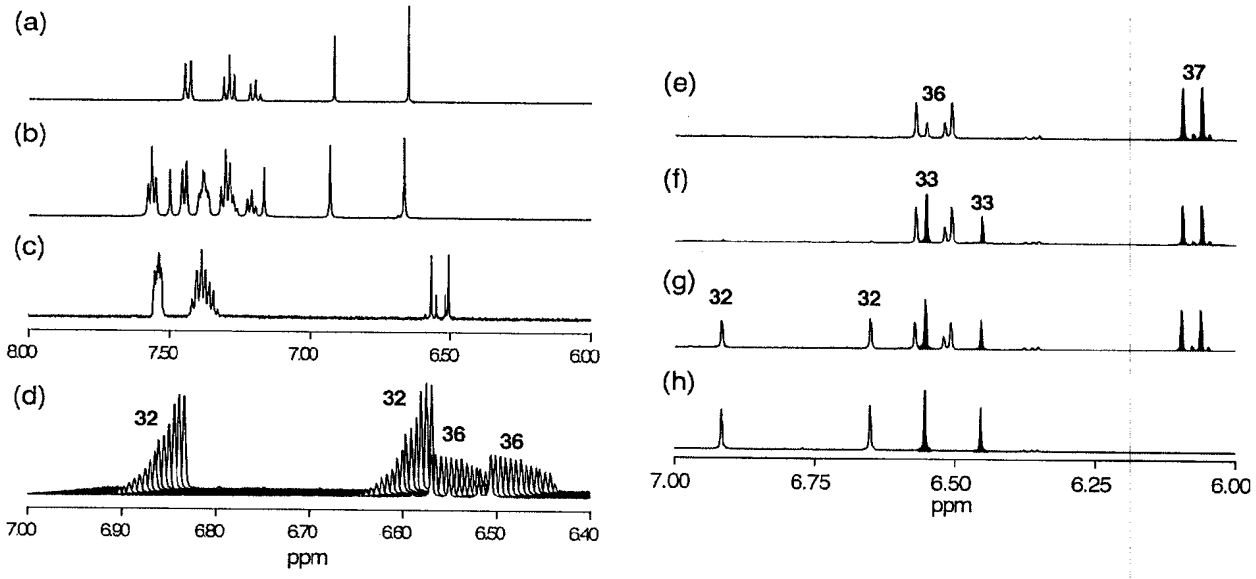

(a)
(b)
(c)
8.00
7.50
7.00
6.50
6.00
(d)
32
32
36
36
7.00
6.90
6.80
6.70
6.60
6.50
6.40
ppm
(e)
36
37
(f)
33
33
(g)
32
32
(h)
7.00
6.75
6.50
6.25
6.00
ppm

Figure 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000862

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07D 333/06*** (2006.01) , ***C07D 333/52*** (2006.01) , ***C09K 9/02*** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 333/06 (2006.01) , ***C07D 333/52*** (2006.01) , ***C09K 9/02*** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN Database, Delphion, Canadian Patent Database, Espacenet,
Search terms: photochrom?, electrochrom?, releas?, switching, reversibly, thermally, hexatriene, conjugated, photoactive,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 5112637 (TOMOEGAWA PAPER CO LTD) 7 May 1993 (07.05.1993) Compounds S-V and T-VII	21-24, 27, 28, 51-53
X	EP 446,717 A (BASF AKTIENGESELLSCHAFT) 18 September 1991 (18.09.1991) pages 5-7 and 11, and Table 1	1, 2, 4, 12-15, 17-19, 21-24, 26-29
X	WO 91/01312 A (TRAZSON LTD) 7 February 1991 (07.02.1991) Figures 1, 2 and 4	1, 2, 4, 12-15, 17-19, 21-24, 26-29, 52, 53
X	NAKAYAMA, YASUHIDE; ET AL: "Thermally irreversible photochromic systems. Photoreaction of diarylethene derivatives with imidazo [1,2-a] pyridine rings" Bulletin of the Chemical Society of Japan (1991), 64(1), 202-207 Abstract, scheme 3	1, 2, 9, 12-14, 17-24, 26-29, 42, 46, 48, 49, 51-54

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 August 2006 (01-08-2006)	12 September 2006 (12-09-2006)

Name and mailing address of the ISA/CA	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001(819)953-2476	May Ling Nung (819) 997-2939

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000862

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OTTO, BERNHARD; ET AL : "Syntheses and UV/Vis properties of amino-functionalized fulgimides" European Journal of Organic Chemistry (2003), (13), 2409-2417 Schemes 3, 4, page 2410-12, Table 2	1, 2, 4, 12-15, 17, 18, 21-24, 26-28, 42, 44-46, 51-54
X	DARCY, PAUL; ET AL: "Photochromic heterocyclic fulgides. Part 2. Electrocyclic reactions of (E)-a-2,5-dimethyl-3-furylethylidene (alkyl-substituted methylene) succinic anhydrides" Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-organic Chemistry (1972-1999) (1981), (1), 202-5 page 202	1, 2, 12-15, 17, 19, 21-24, 26, 27, 29, 42, 46, 51-53
X	HELLER, HARRY G; ET AL: "The design and development of new thermally stable infrared active photochromic compounds" Molecular Crystals and Liquid Crystals Science and Technology, Section A; Molecular Crystals and Liquid Crystals (1997), 297, 73-80 Abstract, page 80, photochromes 21 and 22	1, 2, 4, 8, 12-15, 17, 18, 21-24, 26-28, 42, 51-53
X	ASIRI, ABDULLAH M. "Synthesis and photochromic properties of E,E,-Bis-a-(2,5-dimethyl-3-furyl) ethylidenesuccinic anhydride and its 2-dicyanomethylene derivative" Kuwait Journal of science and engineering (1999), 26(2), 283-288. Schemes 1 and 2	1, 2, 4, 12-18, 21-28, 42, 46, 51-53
X	BADLAND, MATTHEW; ET AL: "Photochromic heteroaromatic thiofulgides and dimethoxybutanoic acid lactones" Chemical communications (Cambridge) (2000), (17), 1567-1568 whole document	1, 2, 4, 12-15, 17, 18, 21, 22-24, 26-28
X	HELLER, H G; ET AL: "Fulgides and fulgimides for practical applications" Molecular Crystals and Liquid Crystals Science and Technology, Section A: Molecular Crystals and Liquid Crystals (1994), 246, 79-86 Compounds 3, 4, 6, 11, 12, 13, 14, 15, 16, 17	1, 2, 4, 12-15, 17, 18, 21-24, 26-28
X	WO 99/31107 A (AMERSHAM PHARMACIA BIOTECH UK LTD) 24 June 1999 (24.06.1999) Examples 1, 2, 3, 6, 9	1, 2, 12-15, 17-19, 21-24, 26-29
X	JP 3264573 (KANEBO LTD) 25 November 1991 (25.11.1991) Tables 1 and 2	1, 2, 12-15, 17-19, 21-24, 26, 27, 42, 46
X	JP 1022872 (YAMAHA CORP) 25 January 1989 (25.01.1989) Abstract, page 4	1, 2, 12-15, 17-19, 21-24, 26-29, 42, 46, 52, 53
X	IRIE, MASAHIRO : "Photochromic dithienylethenes for molecular photonics" Phosphorus, Sulfur and Silicon and the Related Elements (1997), 120 & 121, 95-106. Pages 99-101, Compounds 3b, 4b, 6b, 7b, 13b, 14b, 15b, 16b, 17b, 19b,	1, 2, 4-7, 9, 12-14, 17-19, 21-24, 26-29, 42, 46, 48, 49, 51 3, 11, 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000862

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HELLER, HARRY; ET AL: "A new class of photochromic compounds exemplified by E-5-dicyanomethylene-4-(dialkyl and dicycloalkyl) methylene [1-(2,5-methyl-3-furyl) and (2-methyl-5-phenyl-3-thienyl) ethylidene] tetrahydrofuran-2-ones" Journal of the Chemical Society, Chemical Communication (1994), (23), 2713-14 the whole document	1, 2, 4, 13-18, 21-28, 42, 46, 52, 53
X	CN 1152110 C (FAN, MEIGONG; ET AL) 2 June 2004 (02.06.2004) the whole document	1, 2, 4, 12-15, 17-19, 21-24, 26-29, 42, 46, 51-53
X	LIANHE, YU; ET AL: "Synthesis and solvent effect on absorption spectra of pyrryl-substituted fulgides" Youji Huaxue (1993), 13(6), 590-596 pages 591-593 and Table 1	1, 2, 4, 12-15, 17, 18, 21-24, 26-28, 42, 46, 51-53
X	JP 2002-265465 A (DAISO CO LTD) 18 September (18.09.2002) the whole document	1, 2, 4, 11-15, 17-19, 21-24, 26-29, 42, 45, 46, 52, 53
X	DELEN'KII, L.I.; ET AL: "Synthesis of 4-hetaryl-5,6-(2,5-dimethyl-3-thienyl)-2-phenyl-4H-thiazines and investigation of their photochromism" Chemistry of Heterocyclic Compounds (2005), 41(1), 86-92. the whole document	1, 2, 4, 8-10, 12-14, 17-19, 21-24, 26-28, 42-44, 47, 50-53
X	WILLNER, I.; ET AL: "Photoswitchable binding of substrates to proteins: Photoregulated binding of α-D-mannopyranose to concanavalin A modified by a thiophenefulgide dye" J. Am. Chem. Soc. (1992), 114, 3150-3151 the whole document	30-36, 39, 41
X	MULDER, A.; ET AL: "Photocontrolled release and uptake of a porphyrin guest by dithienylethene-tethered β-cyclodextrin host dimers" Chemistry–A European Journal (2004), 10, 1114-1123. scheme 1; page 1116, right column; page 1120, right column	30-36, 39, 41
P,X	WO 06/037279 A (AKIRAM TRADING LTD) 13 April 2006 (13.04.2006) Figure 1, structure 2; Figure 5, structure 6	1, 2, 4, 12-15, 17-19, 21-24, 26-29, 42, 45, 46, 51-53
Y	WO 04/015024 A (SIMON FRASER UNIVERSITY) 19 February 2004 (19.02.2004) cited in the application see the whole document	3, 11, 20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2006/000862

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. [X] Claim Nos. : 30-40
because they relate to subject matter not required to be searched by this Authority, namely :

see extra sheet (page 7)

2. [X] Claim Nos. : 21-25, 27-41, 51-58
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

see extra sheet (page 7)

3. [ ] Claim Nos. :
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box II

Box II.1
Claims 30-40 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. Regardless, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claims 33-35.

Claims 30-40 are directed to a method of selectively releasing a releasable agent, however, said method would have a therapeutic effect especially as stated in claims 34 and 39 where said carrier compound is delivered to a target location located *in vivo* and said releasable agent is a therapeutic agent or biochemical effectors. Therefore, said claims are directed to a method of medical treatment.

Box II.2
Claims 21-25, 27- 41 and 52-58 are directed to a chemical compound, however, these claims include broad and unclear terms, for example, "charge transfer moiety", "electron donor" and "electron acceptor" and functional definitions, for example, "compound comprises switching moiety reversibly convertible between a first thermally unstable form and a second thermally stable form in response to a light or an electrical stimulus", "aldehyde or a ketone capable of reacting with an activated methylene in a dehydration or deoxygenation reaction" and "diene capable of reacting with a dienophile in a condensation reaction". These functional definitions provide no technical information about the nature of the compound of interest.

Claims 30-40 are directed to a method of selectively releasing a releasable agent, however, these claims include broad terms, for example, "precursor" and "releasable agent" and a functional term, namely, "compound comprises a switching moiety reversible convertible between a first thermally unstable form and a second thermally stable form in response to a light or an electrical stimulus".

Claim 51 is directed to a method of testing for the presence of a target compound in a sample, however, the claim includes broad and unclear terms such as "photochemically inert precursor compound", "target compound" and "photoactive hexatriene reaction product".

The use of these broad terms and functional definitions in said claims is considered to lead to a lack of clarity within the meaning of Article 6 PCT. Apart from the resulting lack of clarity, it also appears that only a small part of the scope of these terms is in fact supported by the description, especially as represented by the specific examples, which only relates to the compounds of the present invention (see formulae I(o) and I(c) and (II)).

At this point, it is impossible to compare the terms or definitions the applicant has chosen to employ with what is set out in the prior art. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, clear and concise, namely, those parts relating to the compounds of formula I(o) and I(c) and (II) with due regard to the general concept underlying the application.

Claims searched completely: 1-20, 26, 42-50, 59
Claims searched incompletely: 21-25, 27-41, 51-58

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Information on patent family members

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